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DYSPITUITARISM

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HISTORICAL

Vesalius was the first to describe the pituitary, and in his "De Corporis Humani Fabrica" he named it the "glans pituitam excipiens"; he believed that this gland secreted the nasal mucus (Πίτυτα, phlegm). However, Galen many years before him knew of this gland, and judging from its well protected location, thought it was of great importance to the human economy. In 1778, Soemmering described it more fully and called it the "hypophysis cerebri." Both Vesalius and Soemmering were of the opinion that the pituitary is a gland; but as they could not find any duct, they considered it a part of the nervous system. Wepfer, Bonnet (1679) and Morgagni found colloid cysts in the pituitary, and Greding (1771) and Melcrave observed and described enlargements of the pituitary. Wenzel claimed that diseases of the pituitary may cause epilepsy; and in the light of present knowledge this is true; for many cases suffering from dyspituitarism have manifested epileptiform seizures.

In 1838, Rathke[1] discovered the dual origin of this gland from the floor of the third ventricle and from a diverticulum of the pharynx (Rathke's pouch). In 1840, Mohr demonstrated the relation of adiposity to tumors of the hypophysis. In 1860, Liégeois,[2] studying the anatomy of this organ, added it to the list of the ductless glands. Marie[3] and Marinesco reported two cases of acromegaly in 1886, and although they were mistaken, in that they thought this disease was due to hyposecretion of this gland, they were the first to draw attention to the relationship between this disease and changes in the hypophysis. About this time Launois described gigantism, and thought that some of these cases may be due to diseases of the pituitary; but it was Cunningham, who, in 1891, had proved that gigantism and acromegaly are the same disease, the only difference being that gigantism was the result of

1. Rathke, H.: Ueber die entstehung der Glandula pituitaria, Arch. f. Anat. Physiol. u. wissensch. Med., 1838, No. 5, 482.

2. Liégeois: Anatomie et Physiologie des glandes vasculaires sanguines, Paris, 1860.

3. Marie, P.: Sur deux cas. d'acromegalie, Rev. de méd., 1886, vi, 297.

pituitary disease in cases where the epiphyseal centers had not yet ossified, and acromegaly in cases where ossification had taken place. In 1899 Oppenheim[4] recognized the importance of x-ray examinations of the sellar region as an aid in diagnosis of tumors of the pituitary. Although Pechkranz correlated adiposity with abnormal skeletal changes, with anomalies of the hypophysis, and although Babinski[5] reported a case of tumor of the pituitary without acromegaly in 1900, Fröhlich[6] is usually given the credit of describing this type of dyspituitarism, in spite of the fact that his communication did not appear until 1901. To Cushing[7] (1909) is due the credit of putting our knowledge of the secretion of the pituitary on a scientific basis; it is he who pointed out and clearly stated the functions of the individual lobes and showed that clinically we may have many different types, depending on whether one or both lobes are hypo- or hypersecreting. In 1912, Burnier[8] collected a group of cases in which dwarfism is associated with hypophyseal symptoms; he refers to them as cases of "Hypophyseal Nanism."

Sir Victor Horsley was the first to publish a personal note regarding the experimental removal of the gland; however, the first actual contribution was made by Marinesco (1892); he concluded that the loss of the whole gland was compatible with life for a long time. The first studies which include any suggestive observations on the symptomatology of a pituitarism were published in 1892, and in 1894 by Vassale and Sacchi; among others who experimented were Cyon, Caselli, Friedmann, Maas and von Eiselsberg.[9] The most important contribution was made in 1908 by Paulesco[10] of Bucharest; he found that removal of the anterior lobe is equivalent to removal of the entire gland (i. e., death in

4. Oppenheim: Discussion, Arch. f. Psychiat., 1901, xxxiv, 303.

5. Babinski, J.: Tumeurs du corpo pituitaire sans acromégalie et avec arrêt de dövelopment des organesgenitaux, Rev. neurol., 1900, viii, 531.

6. Frölich, A.: Ein Fall von Tumor der Hypophysis Cerebri ohne Akromegalie, Wien. klin. Rundschau., 1901, xv, 883.

7. Crow, S. J., Cushing, H., and Homans J.: Experimental Hypophysectomy, Bull. Johns Hopkins Hosp., 1910, xxi, 127; Effects of Hypophyseal Transplantation, Quart. Jour. Exper. Physiol., 1909, ii, 389; Cushing, H.: Sexual Infantilism with Optic Atrophy in Cases of Tumor Affecting the Hypophysis Cerebri, Jour. Nerv. and Ment. Dis., 1906, xxxvi, 704; The Hypophysis Cerebri: Clinical Aspects of Hyperpituitarism and of Hypopituitarism, Jour. Am. Med. Assn., 1909, liii, 249; Partial Hypophysectomy for Acromegaly, Ann. Surg., 1909, l, 1002; The Functions of the Pituitary Body, Am. Jour. Med. Sc., 1910, xxxix, 473; 1913, cxlv, 313; Diseases of the Pituitary, 1912; Cushing H., and Goetsch, E.: Concerning the Secretion of the Infundibular Lobe of the Pituitary Body and Its Presence in the Cerebrospinal Fluid, Am. Jour. Physiol., 1910, xxvii, 60.

8. Burnier: Hypophyseal Nanism, Ann. Ophthal., January, 1912.

9. Eiselsberg, F. v.: Discussion Wien klin. Wchnschr., 1909, xxii, 287; Operations on the Hypophysis, Tr. Am. Surg. Assn., 1910, xxviii, 55; Am. Surg., 1910, lii, 1; Arch. Chir., 1912.

10. Paulesco, N. C.: L'hypophyse du cerveau, Paris, 1908, Vigot Frereo.

twenty-four hours); that loss of the posterior lobe led to no appreciable disturbances, and that separation of the stalk from the base of the brain amounted to a complete or nearly complete removal, as the case might be. In the same year (1908) appeared the notable work of Herring[11] on the anatomy and the histology of the pituitary.

The first operations on the hypophysis were by Horsley;[12] the operative procedure in attacking the hypophysis has been studied on cadavers by Lowe and Koening, Jr., but has been cleared essentially by Schloffer,[13] who also operated on the first patient on the continent in March, 1907.

ANATOMY OF THE PITUITARY

The pituitary body is found in all vertebrates; the development of this gland begins very early in embryonic life. The pituitary is a small reddish-gray, vascular mass of an oval form, situated in the sella turcica, where it is retained by a process of dura mater; this process covers the sella turcica and has a small hole in its center through which the infundibulum passes. The pituitary has a dual origin, the cerebral part develops from a hollow protrusion which comes down from the floor of the third ventricle; the ectodermic portion originates from a diverticulum of the pharynx (Rathke's pouch) which passes upward and unites with the cerebral portion to form the adult gland. As development goes on the anterior or lower part of the closed sac becomes thickened, forming the anterior part of the pituitary body. A more or less definite cleft separates this portion from the posterior lobe, which is composed of the cerebral portion and of the upper portion of the primitive closed sac; these two parts become closely adherent and remain functionally associated; thus the neural part becomes surrounded by an intimate epithelial investment possessing a different histological picture from that which characterizes the anterior lobe, though the two are of ectodermic origin. The epithelial investment of the posterior lobe, together with its upward extension on the outer walls of the infundibular stalk, is designated the pars intermedia. During fetal life the posterior lobe contains a cavity which communicates through the infundibulum with the cavity of the third ventricle; in the adult it becomes firmer and more solid, and the cavity is replaced by lymph-channels, surrounded by cells; these lymph-channels empty directly into the cavity of the third ventricle.

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11. Herring, P. T.: The Histological Appearance of the Mammalian Pituitary Body, Quart. Jour. Exper. Physiol., 1908, i, 121; The Development of the Mammalian Pituitary and Its Morphological Significance, Ibid., p. 161; A Contribution to the Comparative Physiology of the Pituitary Body, Ibid., p. 261.

12. Horsley, V.: On the Technic of Operations on the Central Nervous System, Brit. Med. Jour., 1906, ii, 411.

13. Schloffer, H.: Zur frage der Operationen an der Hypophysis, Beitr. z. klin. Chir., 1906, l, 767.

In the cat the posterior lobe retains throughout life its original cavity in free communication with the third ventricle of the brain; the parts which are derived from the buccal epithelium form an almost complete investment for the nervous portion, and the original lumen of the epithelial pouch also persists throughout life in the form of a well-marked cleft.

The pituitary of the monkey more closely resembles that of man, and is a type in which greater fusion of the original elements from which it has developed has taken place. The posterior lobe is solid throughout. Its investment by the epithelial portion is not so complete as it is in the cat, and only a small cleft remains as the representative of the original buccal pouch.

The pituitary in man is therefore composed of a large anterior lobe (pars anterior), composed entirely of epithelial tissue; of a posterior lobe (pars nervosa) which is of neural origin, and of an intermediate portion (pars intermedia), which, though of neural origin, becomes invested by and intimately fused with a portion of the epithelial sac.

The anterior lobe consists of large granular cells and numerous blood-vessels; the protoplasm of some of these cells being receptive to eosin, some to hematoxylin and some barely staining at all; it is a gland producing an internal secretion, which is poured directly into the blood. The pars intermedia is composed largely of neutrophilic elements. The posterior lobe is made up of two structures; of these the part developed from the brain and consisting of neuroglia and ependyma cells and fibers acts as a framework; it is more or less surrounded and invaded by epithelium which probably furnishes its active part; the secretion passes into the lymph-vessels and is destined to enter the ventricles of the brain.

The pars anterior is very vascular,[14] and the pars nervosa is poor in blood-vessels. The anterior lobe receives its blood-supply from about eighteen or twenty small arteries which converge toward the stalk from the various components of the circle of Willis; these vessels immediately break up into numerous large sinusoidal spaces, in apposition with the cells, and are lined only by endothelium; hence there are no veins or arteries proper in the anterior lobe.

The pars intermedia derives its supply from the vessels of the stalk, from the adjacent brain and from the posterior lobe. The posterior lobe receives its arterial supply from a small artery formed by the union of symmetrical branches from each internal carotid.

According to Creutzfeldt,[15] the hypophysis in the new-born is cylindrical, and its dimensions are, sagittal diameter 5 mm., frontal 9 to 11 mm., vertical 2 mm., and its weight is 90 to 150 mg.; at 10 years it

14. Dandy, W. E., and Goetsch, E.: The Blood-Supply of the Pituitary Body, Am. Jour. Anat., 1911, ii, 137.

assumes a more oval form, mostly due to growth of anterior lobe; it continues to grow to 30 years, is stationary until 40 to 50 years, and then begins to decline. In adults it has an oval form and is larger in women than in men; its weight is 550 to 800 mg.; the sagittal diameter is 6 to 10.5 mm., the frontal 10 to 14.5 mm., and the vertical 5.9 to 9.75 mm.

Erdheim and Stumme[16] examined 150 glands of pregnant women; they noted a color change from gray-red to white, and an increase in size and weight of the structure (900 to 1,800 mg.).

EXPERIMENTAL DATA

The researches of Goetch, Cushing, Jacobson,[17] Crowe and Homans,[7] and Weed, Cushing and Jacobson,[18] have put our knowledge of the physiology of the pituitary on a firm foundation. On the whole, they were able to confirm the findings of Paulesco. They discovered that total removal of the gland in adult dogs causes death in two or three days, with symptoms of cachexia hypophysipriva; in puppies death does not follow for ten days (three to twenty). The symptoms of cachexia usually do not appear for twenty-four to forty-eight hours after the removal of the gland; a marked diminution of urinary output, even to anuria and a transient glycosuria may occur immediately after operation in adult dogs; and in puppies a post-operative polyuria has been often observed, contrasting with the opposite condition seen in the adult dogs. The symptoms of cachexia are unsteadiness of gait and lowered body temperature; an awkward arching of the back, with incurvature of the tail is characteristic; later there is still further fall of temperature, slow respiration, slow pulse, irregular muscular contraction, tremors, lethargy, anesthesia, coma and death; the temperature just before death may fall 20 C. Grafts in cases of total removal cause a distinct prolongation of life through this means.

The effects of posterior lobe removal are inconclusive; some of the dogs had convulsive attacks with maniacal excitement and persistent erotomania.

The results of partial removal of the anterior lobe are the same if the posterior lobe is removed also. In puppies such removal leads to

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15. Creutzfeldt, H. G.: Ein beitrag zur normalen und pathologischen Anatomie der Hypophysis Cerebri des Menschen, Jahrb. d. Hanb. Staatskrankenanst, 1909, xiii, 273; Drie Falle von Tumor hypophyses ohne Akromegalie, Ibid, 351.

16. Erdheim, J., and Stumme, E.: Ueber die Schwangerschaftsveränderung der Hypophyse, Beitr. z. path. Anat. v. z. allg. Path., 1909, lvi, 1.

17. Goetsch, E., Cushing, H., and Jacobson, C.: Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri, Bull. Johns Hopkins Hosp., 1911, xxii, 165.

18. Weed, L. A., Cushing, H., and Jacobson, C.: Further Studies on the Rôle of the Hypophysis in the Metabolism of Carbohydrates, Bull. Johns Hopkins Hosp., 1913, xxiv, 33.

infantilism; the animals remain undersized and the secondary sexual characteristics do not develop; there is also a tendency to hypotrichosis and to subnormal temperature. In adult dogs partial removal causes adiposity, sexual degeneration, subnormal temperature, hypotrichosis, polyuria and somnolence or restless playfulness.

Total removal of the anterior lobe causes death in sixty-eight hours with symptoms of cachexia; the consequences of stalk separation are equivalent to a total or nearly total hypophysectomy.

They also found that repeated injections of the entire gland cause a rapid loss of weight in puppies and in adult dogs; in cases of anterior lobe insufficiency injections of anterior lobe extract cause a thermic response (2 to 4 C.).

The occasional appearance of glycosuria after hypophysectomy had led these observers to further study along this line. They noticed that removal of the posterior lobe and part of the anterior lobe causes a primary fall and a subsequent rise above the normal in the assimilation limit for sugars; that removal of part of the anterior lobe, however, produces little or no alteration in the carbohydrate assimilation limit; the removal of posterior lobe alone causes no primary glycosuria, unless there is considerable traumatism of the stalk, but there is an increased sugar tolerance; this increased tolerance can be brought down to normal by giving posterior lobe extract, 1/20 gm. subcutaneously, 1/80 gm. intravenously; or 2/5 gm. by mouth. In man the normal limit for glucose by mouth is 150 gm., and for levulose 100 gm. It will be seen that in cases of posterior lobe insufficiency there is an increased sugar tolerance; such patients can take as much as 400 gm. of glucose without appearance of glycosuria.

To summarize, we may say that total removal of the gland, or total removal of the anterior lobe, causes death in two or three days, with symptoms of cachexia. Anterior lobe insufficiency in puppies caused adiposity, skeletal infantilism and failure in appearance of the secondary sexual characteristics; in adult dogs anterior lobe insufficiency causes adiposity and sexual degeneration. The symptoms of posterior lobe insufficiency are increased sugar tolerance, subnormal temperature, hypotrichosis, dry skin, low blood-pressure, adiposity and large appetite.

RELATION OF DIABETES INSIPIDUS TO DYSPITUITARISM

It has long been recognized that polyuria with the appearance of dextrose in the urine is a not infrequent accompaniment of acromegaly; but it is only within the last year that both experimental and clinical evidence has accumulated to prove that diabetes insipidus is probably due to disturbed secretion of the pituitary.

In 1674 Thomas Willis first recognized a distinction between two forms of diabetes, a saccharine and a non-saccharine. Claude Bernard discovered his so-called diabetic center in 1849; this point is situated in the floor of the fourth ventricle, between the centers of the pneumogastric and the auditory nerves; puncture at a point a little lower, causes simple polyuria, while puncture at a point a little higher in the frontal direction causes albuminuria.

Author's patient with hypopituitarism.

Cushing found that after certain experimental manipulations of the canine hypophysis, a postoperative polyuria was of frequent occurrence: in adults oliguria rather than diuresis follows a total extirpation; in younger animals there was diuresis. On the other hand, in a series of partial extirpations, postoperative polyuria was almost always observed. Experiments support the view that the clean-cut posterior lobe removals elicit polyuria with the greatest regularity. Schäfer found that posterior

lobe substance given by mouth increases the urinary output; the experimental polyurias have therefore been brought about either by a direct hypophyseal insult, by the injection of extracts, or by glandular implantations. An hypophyseal diuresis may also be elicited by nerve stimulation.

A review of the clinical histories included in many of the past articles on diabetes insipidus makes it clear that a large per cent. have shown symptoms found in lesions involving the base of the brain; a gummatous meningitis affecting the structures in the middle cerebral fossa being a particularly common accompaniment of the disorder. Fuchter and Frank have emphasized the surprising frequency with which primary optic atrophy, often with bitemporal hemianopsias which accompany the encephalitic polyurias, are classified as diabetes insipidus. Kohler in seven of his twenty-two cases of diabetes insipidus found an affection of the infundibulum; Oppenheim in thirty-six patients with basilar luetic meningitis observed polyuria in twelve; Kruse in thirty-four cases of bitemporal hemianopsia noticed diabetes insipidus in seven cases; Oppenheim in two cases of general cerebral symptoms with double temporal hemianopsia and diabetes insipidus found on autopsy a gumma in the region of the chiasma in one case, and a gummatous meningitis in the region of the chiasma in another; in 1882 Hagenbach found a tubercle in the infundibulum of a girl (4½ years old) who had suffered a good deal from thirst and polyuria; in 1903 Rosenhaupt reported a case of diabetes insipidus in which a sarcoma of the anterior lobe of the hypophysis was found; in 1913 Frank reported a case of diabetes insipidus, due to a metastatic carcinoma of the hypophysis, and Simmond reported a case due to a gunshot wound of the hypophyseal neighborhood. The evidence, both experimental and clinical, is therefore in favor of the view that diabetes insipidus is probably a manifestation of dyspituitarism.

THE NERVOUS CONTROL OF PITUITARY SECRETION

Recent studies by Dandy demonstrated the presence of non-medulated fibers coursing from the carotid plexus into both lobes of the pituitary body. This histological demonstration of a sympathetic nerve supply to the gland spoke in favor of a possible nervous influence over its secretion. This discovery led Weed, Jacobson and Cushing[18] to study the nervous control of pituitary secretion, and to further studies on the rôle of the hypophysis in the metabolism of carbohydrates. They found, "provided there is a storage of glycogen available for discharge," that:

1. A piqûre of the hypophysis in the rabbit is comparable in its glycosuric response to piqûre of Bernard's so-called sugar center in the fourth ventricle.

2. Stimulation of superior cervical ganglion by faradization, or even by the manipulation necessary for its exposure, causes glycosuria in the rabbit, cat and dog.

3. Stimulation of the superior cervical ganglion, after exclusion of all possible downward impulses to the abdominal viscera by way of the vagi, cervical sympathetic trunks, or spinal cord, leads to glycosuria.

4. Stimulation of the superior cervical ganglion, after separation of all synopses of the sympathetic system by administration of nicotin, causes glycosuria.

5. Direct faradic stimulation of the hypophysis itself, by a transphenoidal operation, gives glycosuria even after preliminary transection of the spinal cord and cervical sympathetic trunks.

6. If the posterior lobe of the hypophysis has previously been removed by operation the usual stimulation of the superior cervical ganglion fails to give glycosuria.

7. Direct faradic stimulation of the hypophysis provokes glycosuria, even after transection of the spinal cord above the splanchnics.

8. A Bernard piqûre will likewise cause glycosuria even after transection of the spinal cord above the splanchnics.

They came to the conclusion that stimulation of the superior cervical ganglion causes a discharge into the blood-stream of the posterior lobe secretion; this substance is presumably carried through the vascular system to the glycogen storehouses of the body, where it inaugurates glycogenolysis.

PHYSIOLOGICAL ACTION OF PITUITARY EXTRACT

Schäfer[19] and Oliver were the first to study the physiological action of pituitary extract; they experimented with the whole gland. They found that watery or salt extracts, even when boiled, raised the blood-pressure and constricted the peripheral blood-vessels. In 1898 Howell observed that the blood-pressure rise was due to posterior lobe extract only, and that when the blood-pressure was raised the pulse was slowed. In 1901 Magnus and Schäfer noticed that the pituitary extract was diuretic, and in 1906 Herring and Schäfer[20] observed that although posterior lobe extract constricts the arteries of the whole body, it dilates the arteries of the kidneys. Wiggers pointed out that the extract slows the heart and increases the amplitude of its contractions; he also observed that it inhibitis the flow of pancreatic juice and is mydriatic. Other writers[21, 22] have discovered that pituitary extract causes contraction of uterine, vesical and intestinal muscles, and that it promotes the secretion of milk. Cushing pointed out that in puppies suffering from hypopituitarism, injections of anterior lobe stimulate growth and cause

19. Schäfer, E. A.: Die Functionen des Gehirnanhanges, Berner Universtatsschriften, 1911, part B; Schäfer, E. A., and Vincent, S.: The Physiological Effects of Extracts of the Pituitary Body, Jour. Physiol., 1899-1900, xxv, 87.

20. Schäfer and Herring, P. T.: The Action of the Pituitary Extract Upon the Kidney, Phil. Tr., London, 1906, cxcix, 1.

21. Bell, W. B.: The Pituitary Body and the Therapeutic Value of the Infundibular Shock, Uterine Atony and Intestinal Paresis, Brit. Med. Jour., 1909, ii, 1609.

22. Biedl, A.: Innere Sekretion, Berlin, 1910.

a thermic rise (2 to 4 C.), and that injections of posterior lobe lead to emaciation and reduced sugar tolerance.

CLINICAL MANIFESTATIONS OF DYSPITUITARISM

In man the clinical manifestations are nearly the same as those found by Cushing in dogs; the symptoms resolve themselves into those due to, (1) hypo- or hypersecretion or perversion of secretion of the gland itself; (2) those due to increased cerebral pressure; (3) those due to the local pressure of the tumor, and (4) those due to the involvement of the other ductless glands.

Deficiency of anterior lobe in children leads to infantilism; there is inhibition of skeletal development. Hypersecretion of the anterior lobe leads to gigantism in cases in which the epiphyseal centers had not yet ossified, and to acromegaly in adults; that gigantism and acromegaly are closely related is evident from the observations of Sternberg;[23] he found that 20 per cent. acromegalics are over 5 feet 10 inches in height, and that 40 per cent. of all giants have some signs of acromegaly. In hyperpituitarism there is hypertrophic alteration of the skin, and increase in size of the hair follicles; there is also hypertrophy of the papillae and activation of the secretory glands; so that the skin becomes greasy and moist; hypertrichosis is marked. Deficiency of posterior lobe is usually associated with adiposity and increased sugar tolerance; the temperature is usually subnormal, and the subjective chilliness and drowsiness indicate diminished metabolism. The skin is usually smooth; may even suggest edema, but does not pit; hair on the scalp may be abundant, but axillary and pubic hair may be entirely wanting; the nails are often small and do not show the crescent at their base; constipation is often obstinate and usually improves on glandular therapy; psychic disturbances are frequent and are usually due to involvement of frontal and temporal lobes. The symptoms of cerebral involvement are, change in disposition, enfeeblement of memory, disorientation and ". . . notable always is the utter lack of appreciation of, and complete indifference to, the existing condition." In hyperpituitarism, temperamental changes, wakefulness, lack of concentration and irritability are more common; in hypopituitarism mild psychoses to extreme mental derangements with epilepsy are not infrequent.

SYMPTOMS OF INCREASED CEREBRAL PRESSURE

These are too well known to need any detailed mention here; they are, in general, headache, general convulsions, double optic neuritis and optic atrophy, change of disposition and of mental power, vomiting, vertigo, changes in the pulse-rate and attacks of syncope; the general

23. Sternberg, M.: Beitrage zur Kenntniss der Akromegalie, Ztschr. f. klin. Med., 1895, xxvii, 86.

symptoms occur irrespective of the location of the tumor and depend on its rapidity of growth, its vascularity and its pathological character. They vary in severity from time to time. When a tumor is growing rapidly they are very severe; if it remains stationary, they may almost disappear. Headache is the most important and constant symptom of brain tumor; it varies in intensity, but is usually severe; general convulsions are the next most frequent symptom of brain tumor; they are particularly liable to occur as an early symptom in children; vomiting is also more frequently observed in children than in adults; it usually occurs without special relation to the time of meals.

NEIGHBORHOOD SYMPTOMS

One of the most important local symptoms is primary optic atrophy; later there is a superimposed optic neuritis due to the growth reaching a large state. There is some distortion in the visual fields in almost all cases; bilateral defects are almost twice as common as homonymous lesions; mere tendencies toward temporal defects must be carefully looked for; particularly defects limited to color peripheries. The primary defect usually first involves the color boundaries alone, in one upper temporal quadrant; this is followed by a more or less complete temporal hemiachromatopsia; in all cases the color fields become involved first, the form fields later; the macular area is often spared for a long time, but finally becomes implicated; rarely are the two eyes affected to the same degree. Abnormal pupillary conditions are often present; a definite hemiopic pupillary response and a negative oculomotor reaction to the prism deflection of an image in the blind half of the retina may be expected when only half blindness is complete. Oculomotor implication is often present, as are also double vision, palsies and nystagmus.

Other nerves may be involved; the individual may have anosmia, trifacial neuralgia and spasticity due to pressure on the central peduncles. Uncinate seizures are surprisingly common and the frontal lobe is not infrequently involved.

He may also have local signs in the nasopharynx, as troublesome epistaxis, intermittent discharge of mucus into the pharynx and in a few a tumor can be seen and felt in the retropharynx.

Among the most important of the local symptoms is deformation of the sella turcica; extreme hypersecretion and hyposecretion may exist with but little if any alteration in the shadow cast by the bony encasement of the gland; the sella may be well preserved, even though the tumor may be enormous and has been of long duration. There are three types of sella deformation; (1) those associated with thickening of the clinoids and dorsum epiphii; (2) those with thinning from pressure absorption of these parts, and (3) those with more or less destruction of

all outlines. Equally important are the abnormally small sellae, which accompany the primary glandular hypoplasias of the young.

SYMTOMS REFERABLE TO OTHER DUCTLESS GLANDS

Although our knowledge of the internal secretions is incomplete and confused, much progress has been made in this branch of medical science in the last decade. One fact has been clearly brought out, and that is that the physiological connection of all the ductless glands is an intimate one, and that in pathological conditions of one of them all the other glands are affected.[24, 25, 26, 27, 28] The influence of one gland on another may be compensatory or inhibitory. The existence of a relationship between the thyroid and the hypophysis is perhaps the most satisfactorily demonstrated of all the possible interrelations of endosecretory organs. Rogowitch has found that after thyroidectomy the pituitary hypertrophies. In Basedow's disease sex functions are often affected; in myxedema there is sex depression. Parchow and Goldstein have concluded that there exists a distinct antagonism between the thyroid and the ovaries. Charrin and Jardy,[29] however, came to the opposite conclusion. Cooper had observed hypertrophy of the thymus in Basedow's disease. In Switzerland the offspring of goitrous mothers have both thymus and thyroids enlarged; thyroidectomy raises the assimilation limit for dextrose, showing the influence of the thyroid on the pancreas. A theory that the adrenals are related to the sex functions was proposed by Meckel (1806); in certain aborted fetuses he had noted that both the adrenals and the gonads were lacking; in animals in which sexuality is marked, the adrenals are notably large; in birds and in amphibia the gonads and the adrenals are closely associated in position. Bullock[30] and Sequeira have been able to find in the clinical literature twelve cases of children showing sexual precocity, who at autopsy were found to have enlarged adrenals; ten of these were females from 2 to 11 years of age. Pansini and Boneanti noticed hypertrophy of the thymus in Addison's disease. Erdheim and Stumme[16] found hypertrophy of the pituitary in pregnancy; the pituitary is normally held in check by secretions of the gonads.

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24. Hopkins, R. G.: The Interrelation of the Organs of Internal Secretion, Am. Jour. Med. Sc., 1911, cxli, 374.

25. Kidd, L. J.: The Pineal Body, Med. Chronicle, 1912, lvii, 154.

26. Sajous: The Internal Secretions, 1912.

27. Tandler, M.: Ueber den Einfluss der innersekretion Anteile der Geschlechtsdrüsen auf die äussere Erscheinung des Menschen, Wien. klin. Wchnschr., 1910, xxiii, 459-467.

28. Vincent, S.: Internal Secretions and the Ductless Glands, London, 1912.

29. Charrin and Jardy: Comp. rend. Acad. d. sc. Paris, 1906, cxlii, 1442.

30. Bullock, W., and Sequeira, J. H.: On the Relation of the Suprarenal Capsules to the Sexual Organs, Tr. Path. Soc. London, 1905, lvi, 189.

	Skeletal Overgrowth	Dwarfism Skeletal Undergrowth	Genital Hyperplasia	Genital Hypoplasia	Sexual Precocciousness	Impotence	Increased Carbohydrate Tolerance	Glycosuria	Hypertrichosis	Hypotrichosis	Mental Precocity	Mental Dulness	Sub-Normal Temperature	High Blood-Pressure	Low Blood-Pressure	Adiposity	Pigmentation	Asthenia	Symptoms of Cerebral Pressure	Sellar Deformation	Rapid Pulse	Tremor
Pituitary—																						
Hypersecretion of anterior lobe.	:	:	:	+	:	+	:	+	+	:	:	+	:	+	+	:	+	+	+	+	+	:
Types, Marie and Launois		:	:	+	:	+	+	:	:	+	:	+	+	:	+	+	+	:	+	+	+	:
Hyposecretion of posterior lobe.																						
Type, Frölich	:	+	:	+	:	+	+	:	:	+	:	+	+	:	+	+	+	:	+	+	+	:
Hyposecretion of both lobes. Type, Burnier	:	+	:	+	:	+	+	:	:	+	:	+	+	:	+	+	+	:	+	+	+	:
Thyroid—																						
Hypersecretion. Basedow's disease.	:	:	+	:	:	+	:	+	:	:	+	:	:	+	:	:	:	+	:	:	:	+
Hyposecretion. Cretinism	:	:	+	:	+	+	+	:	:	+	:	+	+	:	+	+	:	:	:	:	:	:
Adrenal—																						
Hypersecretion	+	:	+	:	+	+	+	:	+	:	:	+	+	+	:	:	+	+	:	:	:	:
Hyposecretion. Addison's disease	:	:	:	+	:	:	:	+	:	:	+	:	:	:	:	+	:	:	:	:	:	:
Pineal—																						
Hypersecretion	+	:	+	:	+	:	:	:	+	:	:	:	:	:	:	:	:	:	:	:	:	:
Gonads—																						
Hyposecretion—	+	:	:	+	:	+	+	:	:	+	:	:	+	:	:	+	:	:	:	:	:	:
Pancreas—																						
Hyposecretion	:	:	:	:	:	:	:	+	:	:	:	:	:	:	:	:	:	+	:	:	:	:

Enough has been stated to substantiate the statement that every disturbance of a ductless gland is really a polyglandular disturbance, and that some of the symptoms present in disturbances of any one of the glands are probably due to the secondary involvement of the other glands.

In studying the table, it will be evident that the presence of any of the following symptoms in any case should arouse our suspicion of a disturbance in the ductless gland system. The symptoms are as follows: Dwarfism or skeletal overgrowth, adiposity or emaciation, sexual precociousness or impotence, hypertrichosis or hypotrichosis, genital hyperplasia or atrophy, mental precociousness or dulness, high or low blood-pressure, glycosuria or increased carbohydrate tolerance, asthenia, pigmentation of the skin and subnormal temperature. This table also shows that, although the same symptom may be present in disturbances of different glands, yet there are symptom-complexes which are pathognomonic and strongly point to the involvement of a particular gland.

The following symptoms present in dyspituitarism are referable to secondary involvement of the other ductless glands: Imperfectly acquired secondary sexual characteristics in cases in which the lesion antedates puberty, and of resultant amenorrhea or impotence with retrogressive sexual changes, when the malady develops after the acquirement of adolescence; pigmentation of the skin, asthenia, low blood-pressure and hypoglycemia point to adrenal involvement.

PATHOLOGY

Disturbances of the pituitary may be primary or secondary, functional or organic. The primary organic disturbances may be due to hyperplasia of the gland, to tumors of the gland or to tumors arising in the neighborhood of the pituitary, and which compress it and alter its secretion; such tumors usually do not cause acromegaly; any tumor of the brain or anything which prevents the secretion of this gland (e. g., hydrocephalus) from entering the third ventricle, may cause symptoms of dyspituitarism.

In 29 cases that were operated or came to autopsy, Cushing found that 23 were due to homoplastic epithelial growths and 6 were heteroplastic; of these, 1 originated from a developmental rest, 2 were teratomas, 2 infundibular cysts and 1 endothelioma. Of 60 cases of acromegaly which came to autopsy, collected by Creutzfeldt,[15] 8.3 per cent. were without any hypophyseal changes; 25 per cent. were sarcoma; 20 per cent. hyperplasias; 13.3 per cent. struma; 20 per cent. adenoma; 1.6 per cent. glioma; 6.6 per cent. no definite diagnosis made. In 55 cases of tumor of the hypophysis, without acromegaly, he found sarcoma in 27.27 per cent.; hyperplasia in 9.09 per cent.; struma in 5.45 per cent.; ade-

noma in 18.18 per cent.; *Platten epitheltumoren,* 34.54 per cent.; teratoma, 1.8 per cent.; lipoma, 1.8 per cent., and metastatic, 1.8 per cent.

CLINICAL TYPES

One of the earliest types to be recognized is acromegaly.[3] This type is too well known to need any detailed description. Closely associated with this type are the cases of gigantism;[31] they are both due to hypersecretion of the anterior lobe; gigantism occurs in cases in which the epiphyseal centers had not yet ossified; whereas, acromegaly usually occurs in adults; still cases of acromegaly have been reported in children by Antonini and Marzocchi, de Cyon,[32] Rake, Salle and others. The most notable symptoms of acromegaly are skeletal overgrowth, *main en large,* phalangeal alteration, mandibular prognathism, spacing of teeth, rounding of shoulders, sternoclavicular enlargement, peculiar cranial configuration and hypertrichosis.

TYPE FRÖHLICH

To this type[6] belong those cases which have neighborhood symptoms of tumor of the hypophysis, without any evidences of acromegaly; these cases have a peculiar adiposity; with a feminine type of distribution of the fat when it occurs in males; there is aplasia of the genitals, hypotrichosis, subnormal temperature, undersized stature, psychoses of varying nature and increased carbohydrate tolerance. These cases are due to hyposecretion of the posterior lobe. Such cases in children have been reported by Fröhlich, Babinski, Hochwart, Uhlthoff, Cagnetto,[33] Erdheim, Israel, Woolcombe, Creutzfeldt, Cushing and others.

TYPES BURNIER

In 1912 Burnier[8] collected a group of cases from the literature and added one of his own cases, which in addition to local signs of hypophyseal tumor and signs of posterior lobe insufficiency, showed marked dwarfism. These cases are due to hyposecretion of both lobes. The most important symptoms of this type are optic nerve atrophy (almost invariably present), adiposity, dwarfism and atrophy of external and internal genitals. Such cases have been recorded by Burnier, Kon, Benda, Hutchinson, Heuter, Bartels, Nazair, Zöllner, Mixter and Quackenboss and others.

TYPE CUSHING

It is Cushing who pointed out that a pituitary may be hypersecreting at one time and hyposecreting at another; and that in fact all cases of

31. Launois, P. E., and Roy, P.: Etude biologique sur les géante, Paris, 1904.
32. Cyon: Prog. méd., 1898.
33. Cagnetto: Virchow's Arch. f. path. Anat., 1904.

hyperpituitarism show evidences of hypopituitarism as the disease progresses. It is he also who made the observation that one lobe may be hypersecreting and the other lobe hyposecreting at the same time; and thus we may have a variety of mixed types. He especially called attention to cases of skeletal overgrowth associated with adiposity and sexual infantilism without acromegaly.

DIAGNOSIS

Diagnosis of acromegaly and gigantism is simple; the Roentgen rays, however, are of great aid. They may show an enlarged sella turcica, or they may show enlargement, broadening and tufting of the phalanges. In posterior lobe insufficiency, the estimation of the sugar tolerance is of importance. We must always suspect posterior lobe insufficiency in individuals who can take more than 150 gm. glucose and 100 gm. levulose by mouth without glycosuria. In some cases of anterior lobe hyposecretion there is a thermic response when they receive an injection of anterior lobe extract. The symptom-complex of skeletal overgrowth or dwarfism, adiposity, genital atrophy, optic nerve atrophy, deformation of sella and increased carbohydrate tolerance are absolutely pathognomonic of dyspituitarism.

TREATMENT

Treatment may be medical, surgical or both; surgical intervention is indicated to relieve general central pressure; to relieve neighborhood symptoms and to implant pituitary gland in cases of hyposecretion. To relieve general cerebral pressure symptoms a subtemporal decompression is indicated; for the neighborhood symptoms, fragmentary extirpation of the tumor or removal of the sellar floor and opening of the capsule are the operations of choice in the absence of pressure symptoms, but when headaches are very severe a sellar decompression should be advised. The medical treatment consists in the application of radium after operation and the administration of whole gland extract by mouth or hypodermically, the dose varying in each case, depending on the amount of posterior lobe insufficiency.

Alex. K., 12 years old, was brought to the Vanderbilt clinic (Pediatric section), by his mother, April 27, 1912. The mother's chief concern was that her son's genitals were very much undeveloped; she also stated that he suffered a great deal from headaches, vertigo, double vision and vomiting, and that he always felt cold.

Family history was negative. A brother of the patient, who had also been treated at the clinic two years previously, was a Mongolian idiot and had died of pneumonia. The birth of the patient was normal; he was breast fed for nine months; he had pneumonia at 5 months and measles at 1 year; suppurative adenitis at 2 years; no other acute illness; for the last two or three years the patient had been complaining of headaches, double vision, vertigo and vomiting; the vomiting was regardless of the nature of food or time of feeding. He was always cold and suffered a good dead from constipation.

Physical examination revealed a very well nourished boy; weight 93½ pounds (normal weight for boy of 12 years is 81 pounds); height 53 inches (that is 4 inches undersized for his age); facies was somewhat peculiar and the expression anxious; slight exophthalmos was present; no enlargement of the thyroid could be made out; chest and abdomen negative; the adiposity was of a feminine type of distribution; the fat folds over the hips, knees and feet were quite marked; the genitals were hypoplastic; there were no axillary nor pubic hair; the fingers were of a peculiar tapering kind; there was a fine tremor of the fingers present; the pulse was 84 to the minute; temperature 97.8 F.; examination of the eyes revealed a bitemporal hemianopsia; mentality was normal; Roentgen ray examination of the hands showed nothing abnormal; that of the head showed slight enlargement of the sella turcica.

May 14, 1912, the patient was given 250 gm. of glucose on an empty stomach, and all subsequent specimens of urine were collected; none showed any sugar; this was repeated three times with the same result; levulose the patient could not tolerate in any form; it was invariably vomited. The patient was given 10 grains of pituitary extract (whole gland) three times a day. The urine was constantly examined while the patient was under treatment and no glycosuria appeared; the temperature, which was subnormal before treatment; never ranged lower than 99 F. after treatment was instituted; the constipation was also much relieved; the pulse ranged from 85 to 100. Under treatment the patient lost 10 pounds in two months; treatment had no effect on the headaches, vertigo or vomiting; a sellar decompression was suggested, but was refused and the patient stopped coming to the clinic.

The presence of genital hypoplasia, hypotrichosis, adiposis, skeletal undergrowth, with symptoms of cerebral pressure and an enlarged sella turcica, led us to conclude that we were dealing with a case of hyposecretion of both lobes (type Fröhlich), probably due to a tumorous growth. The presence of slight exophthalmos, tachycardia and tremor suggest the presence of hyperthyroidism, which is secondary and probably of a compensatory nature, as the thyroid and the pituitary are synergic.

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A STUDY OF THE WASSERMANN REACTION IN ONE HUNDRED INFANTS*

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In an article entitled "The Wassermann Reaction in Children and Infants," Churchill[1] states that a positive serum reaction was found in thirty-nine of 101 children examined. The cases were taken "mostly at random" from a large hospital for children. There was a family or past history of syphilis, or signs of the disease, together with a positive serum reaction in twenty-nine of these cases. In the ten other cases, the serum reaction was positive without a history of or evidences suggestive of syphilitic infection. The technic used in some of the cases was that recommended by Wassermann, but in the majority the Noguchi modification was employed. Churchill was surprised to find so large a number of positive serum reactions in children apparently free from syphilis, but he wisely suggested that further studies were necessary before valid conclusions as to the incidence of latent hereditary syphilis could be drawn.

AUTHORS' INVESTIGATION

In this investigation the sera from 101 infants, irrespective of the reason for which they were in the hospital, were tested. The technic employed was that advocated by Wassermann, and in forty-three instances this was supplemented by tests made according to the method of Noguchi. The blood was procured by means of the suction apparatus described by Blackfan.[2] The collection, from infants, of blood for the Wassermann test has always been attended with difficulty, but by the use of this method a sufficient quantity for both tests was easily obtained. Effort was made to collect all data that might aid in establishing a diagnosis of hereditary syphilis.

Group I.—In this group there were 68 infants from a large foundling hospital. The youngest child was 5 days old, and the oldest was 29 months; 20 were under 6 months, 24 under 12 months, 16 under 24 months and 8 between 24 and 29 months.

* Submitted for publication May, 1913.

1. Churchill, F. S.: Jour. Dis. Child., 1912, iii, 363.
2. Blackfan, K. D.: Jour. Dis. Child., 1912, iv, 33.

The family history could not be obtained in the majority of cases. The *past history* and *physical examination* failed to show in a single instance any evidences of hereditary syphilis. Of the 68 infants tested, 44 were normal and well nourished, 19 were slightly rachitic, 2 had Hirschsprung's disease, 1 had icterus neonatorum, 1 had tetany and 1 had meningitis (probably tuberculous).

Group II.—There were 33 infants in this group, from the wards and the out-patient department of the St. Louis Children's Hospital. The youngest child was 2 weeks of age and the oldest was 30 months; 9 were under 6 months, 10 under 12 months, 12 under 24 months and 2 between 24 and 30 months.

The family history was known in all of the cases except one, an illegitimate baby 2 weeks old. It had no bearing on the question at hand in 29. In the remaining 3 cases, there were certain facts suggestive of syphilis. In Case 32, the mother had had one miscarriage and in Case 31, the mother had had two miscarriages. In Case 33, to which reference will be made later, besides the family history, the past history and physical examination were also suggestive of syphilis. *The past history and physical examination* of 32 infants in this group presented no evidences of syphilis. The cases studied included children with:

Nutritional diseases	18
Severe burn	1
Bronchitis	1
Eczema	1
Pyelocystitis	1
Pneumonia	3
Idiocy, Mongolian	1
Tuberculosis, pulmonary	1
Spastic Paraplegia	2
Normal	4

RESULTS OF THE SEROLOGICAL TESTS

Of the 68 infants comprising Group I, the Wassermann test showed *no fixation* of complement in 66. These 66 cases do not require further consideration inasmuch as the clinical findings failed to show any evidence of syphilis.

Of the remaining 2 infants, there was slight fixation of complement in the serum from one by both the Noguchi and the Wassermann method. This infant (No. 68), 29 months old, was well nourished and there was no reason from the past history or physical examination, to suspect hereditary syphilis. The serum was tested at three different times, and each test gave slight fixation. As there were no clinical evidences of syphilis and as the fixation test at no time was definitely positive, a diagnosis of hereditary syphilis could not be made. The case of the other infant (No. 67) is of interest because no clinical evidences of latent hereditary syphilis were found and the serum caused complete fixation of

complement. This child, 28 months old, was well developed and well nourished, and had been in the institution since birth. The blood was tested repeatedly, and each time showed complete fixation by both the Noguchi and the Wassermann methods. In view of our present knowledge regarding the specificity of the Wassermann reaction, this establishes the case as one of hereditary syphilis in spite of the lack of confirmatory clinical signs.

Of the 33 infants composing Group II, the Wassermann test showed *no fixation* of complement in 32, and *complete fixation* of complement in 1.

The infant (No. 33) whose serum showed complete fixation of complement presented signs of syphilis when admitted to the hospital. The mother had had one miscarriage and one still-birth. The baby had had, a few weeks after birth, the snuffles and a desquamation of the skin from the palms of the hands and the soles of the feet. On admission at 6 months of age, the patient, who was undernourished and poorly developed, weighed 7½ pounds. The spleen was enlarged and the superficial lymph-nodes were palpable. This, without question, was a case of hereditary syphilis.

GROUP I

Case No.	Family History	Past History	Phys. Ex.	Wassermann
1-66	Not known	Negative	Negative	No fixation
68	Negative	Negative	Negative	Partial fixation
67	Negative	Negative	Negative	Complete fixation

GROUP II

Case No.	Family History	Past History	Phys. Ex.	Wassermann
1-30	Negative	Negative	Negative	No fixation
31	2 miscarriages	Negative	Negative	No fixation
32	1 miscarriage	Negative	Negative	No fixation
33	1 miscarriage 1 stillbirth	Snuffles Desquamation	Palpable Spleen	Complete fixation

To recapitulate: In Group I there were 68 children, none of whom gave, on investigation of their family or past history or by physical examination, any evidence of hereditary syphilis. The Wassermann reaction was negative in 66, doubtful in 1 and positive in 1. The Noguchi modification was made in 43 of the cases in this group, and verified the results of the Wassermann test; i. e., 41 sera were negative, 1 was doubtful and 1 was positive.

In Group II no clinical evidences of hereditary syphilis were found in 30 infants. In 2 infants the family history was suggestive. In 1 infant, the family and past history and the physical examination were suggestive of syphilis. The Wassermann reaction was negative in 32 of the infants and positive in 1 infant.

These findings are not surprising. They confirm the already established fact that in the majority of patients in which the family and past history and the physical examination are negative, the serum reaction is

likewise negative. In the same manner a positive reaction in the serum of a patient with signs of the infection, as is shown by Case 33, is to be expected.

That a child without clinical evidences of syphilis, but whose serum gives a positive Wassermann reaction, may still be syphilitic, is not a new disclosure, for it has long been recognized that hereditary syphilis may remain latent for an undetermined period, and become manifest at a later date. Case 67 is such an instance and emphasizes the great value of the Wassermann test.

The significance of a so-called partial or weak reaction, like that obtained with the serum from Case 68, is not perfectly clear, and judgment as to the nature of the case should be deferred. Observation of the patient and frequent repetitions of the test, must teach the meaning of this type of reaction as an aid to the diagnosis of hereditary syphilis.

Regarding the incidence of latent hereditary syphilis as determined by means of the complement fixation test, larger series of cases must be studied and much more information obtained before definite conclusions can be drawn. The finding by us of one case of latent hereditary syphilis is at variance with Churchill's results, but that this difference is more apparent than real, is evident from an analysis of the cases in his Group V. In this group of his are included children without definite signs of syphilis and without a suggestive history, but with a positive serum reaction. He states that "there is no ground, except a positive serum reaction, for regarding four in this group (Nos. 1, 12, 20 and 31) as cases of syphilis." It seems to us that these should be regarded and classified as cases of latent hereditary syphilis. The positive serum reaction can be explained only on this basis, and a failure to accept this explanation must be taken as an admission of doubt as to the specificity of the complement fixation test, or as an acknowledgment of some error in technic. It would be interesting to know the future history and clinical course of these patients.

The results of this series, in which only two cases gave a positive serum reaction, are strikingly low as compared with the thirty-nine positive cases found by Churchill and consequently do not confirm his observations regarding the frequency of hereditary syphilis among hospital children. Several factors concerning the complement fixation test should be kept in mind as a possible explanation for such a wide variation, viz., the hypersensitiveness of the Noguchi as compared to the Wassermann technic; the personal element present in the interpretation of the reaction and the possibility of error in technic.

These two investigations show conclusively that small series from different sources give widely divergent results, and that further studies of larger series of cases are necessary in order to determine the prevalence of hereditary syphilis among hospital children.

THE WASSERMANN REACTION IN HEREDITARY SYPHILIS, IN CONGENITAL DEFORMITIES AND IN VARIOUS OTHER CONDITIONS IN INFANCY

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There is probably no modern means of diagnosis of greater importance than the Wassermann reaction. This not only enables one to be certain of the existence of syphilis in many doubtful conditions, but also to exclude syphilis in many cases where formerly it was suspected. It is the consensus of opinion at present that latent as well as active syphilis gives a positive response to this test. It is also the general belief that children who react positively should receive the benefit of antisyphilitic treatment.

Like all laboratory reactions, the Wassermann test is not infallible. Positive reactions may be obtained in certain cases of scarlet fever and in infection with trypanosomes; but neither of these conditions is very likely to be confused with syphilis. Negative reactions may be met with in syphilitic cases as a result of treatment, whether by mercury or salvarsan, and occasionally in other cases for unexplained reasons. With proper technic the errors are chiefly on the negative side, but they are not numerous. Errors due to faulty technic must also be taken into account. These are much more common and are almost always on the positive side, so that the children tested are pronounced syphilitic when they are not so. It is absolutely essential that reagents used should be right; that the antigen be good and well tested; and that sheep or human corpuscles be fresh, preferably less than twenty-four hours old, and properly washed. A mistake in technic is the probable explanation of the large percentage of positive reactions obtained in children by some writers. One person with such an experience has, indeed, recently written to me raising the question whether the Wassermann test can be relied on in infants. It had been used on those who were to be placed out for adoption and the number of positive reactions obtained was most disturbing. Under such circumstances doubt should be cast on the manner in which the test was made, rather than on the value of the test itself.

It was to answer the question as to the frequency of active or latent syphilis in the ordinary run of hospital infants as well as in some special

conditions, particularly congenital deformities, that a series of observations has been carried on in the Babies' Hospital during the past year and a half.

The Noguchi modification of the Wassermann test has been employed in all of our patients. This has the great advantage, in the case of infants, of requiring much less blood (only ½ of a c.c.) than the Wassermann test. All of these tests, with the exception of those in the last group of seventeen children examined, have been made at the Rockefeller Institute by one of Dr. Noguchi's assistants and under his supervision. I think we may, therefore, be certain as to the reliability of the technic and the accuracy of the observations.

During the period mentioned, 34 cases of hereditary syphilis were admitted for treatment. In 31 of these, blood tests were made, and 30 gave a positive reaction. The single case not responding was in an infant 5 months old, in whom there was a typical history of syphilis, but the child had been treated regularly with inunctions of mercury for a period of three months before.

Previous treatment with mercury does not seem to affect the reaction unless it has been continued for a considerable time and with regularity. For of the 30 patients giving positive reactions, 9 had been treated with mercury as follows: One an infant 6 months old, for two weeks; two sisters of 4½ and 22 months, irregular treatment with inunctions since birth; one infant of 6 weeks, inunctions since it was 4 days old; one child of 2½ years, inunctions irregularly from birth; one infant of 7 months, inunctions and mercury internally for one week; one infant of 21 months, irregular inunctions and potassium iodid almost from birth; one child of 2½ years, irregular inunctions from birth. If we adopt the ordinarily accepted view that a positive Wassermann reaction is an indication that the patient is not cured and still requires treatment, it will be evident from the cases just cited how incomplete and how uncertain is the cure of syphilis effected by mercury and potassium iodid.

Of children who were not regarded clinically as syphilitic, 178 were studied. While this number is not large, it should be remembered that these cases were selected from about 1,800 hospital admissions, and that they include, in the first place, nearly every child in whom even a slight suspicion of syphilis existed. Besides, a considerable number of infants suffering from marasmus or malnutrition without selection were examined, all cases with congenital malformations, and a miscellaneous group of various acute and chronic diseases also unselected. Of the 178 tested, 167 gave negative reactions, and 11 positive reactions. The ages of the children were as follows:

	Positive	Negative	Total
Under 6 months	5	85	90
6 to 12 months	2	33	35
1 to 2 years	3	33	36
Over 2 years	1	16	17

Positive Cases.—Of eleven children showing no definite clinical evidence of syphilis, but giving a positive reaction, six died and came to autopsy. Four of these showed perisplenitis and perihepatitis of sufficient degree to warrant a pathological diagnosis of syphilis. Three of these were marasmus infants. In one of them there could be discovered no family history suggesting syphilis; in one the mother had had three previous miscarriages; in a third there was one previous miscarriage, but otherwise a negative family history; in a fourth, a child dying of acute gastro-intestinal intoxication, the parents gave a definite history of syphilis, and the child had general glandular enlargements. In only one case giving a positive reaction which came to autopsy, did the family history, the examination of the patient, or post mortem findings give no suggestion of syphilis.

Of the six positive cases which terminated in recovery, two were in rachitic infants with moderate enlargement of the liver and spleen; one was a child with spastic diplegia, whose mother gave a positive reaction; one was a case of sclerema, with moderate enlargement of liver and spleen, but with a negative family history; one was a cretin with a negative family history, and one, a child admitted for convulsions of unknown origin. The positive reaction in the infant last mentioned led to tests of both parents, but neither responded. There was nothing in this patient's symptoms to suggest syphilis.

We have, therefore, in this group of eleven cases, only three in which no evidence of syphilis could be found, either in the family history, the clinical symptoms or the pathological findings. In the remaining eight positive cases, the evidence of syphilis was practically conclusive in five; in the other three cases, rickets and enlarged liver and spleen were present.

Negative Cases.—One hundred sixty-seven children gave a negative reaction. In this group, twelve came to autopsy and in none of them were any lesions present suggestive of syphilis. The largest single group were fifty-six infants with malformations or congenital deformities. Inasmuch as syphilis has been thought to be an etiological factor in certain of these conditions they were made a subject of special study. These cases were as follows:

Spina-bifida	10	Defective cerebral development	6
Mongolian idiocy	8	Cystic kidney	1
Spastic diplegia	6	Hygroma of the neck	1

Congenital cardiac disease	6	Congenital obliteration of the bile ducts	1
Hare-lip and cleft palate	5	Amaurotic family idiocy	1
Hydrocephalus	5	Clubfeet and hands	1
Exstrophy of the bladder	1		
Microcephalus	4	Total	56

The remaining cases were divided as follows:

Marasmus and malnutrition	57	Rachitis	3
Acute pneumonia	16	Tumor of the brain	2
Empyema	5	Chorea	2
Tuberculosis	7	Duodenal ulcer	3

And one each of the following conditions: Pemphigus neonatorum, meningeal hemorrhage, scurvy, leukemia, diabetes, encephalitis, poliomyelitis, papilloma of the larynx, chronic nephritis, eczema, basilar meningitis, acute arthritis, hernia, convulsions, ulcerative stomatitis, hydrocephalus. Total, 111.

From these observations it would appear that syphilis does not play an important part in the production of the common congenital deformities, since in not a single one of fifty-six consecutive cases studied was a positive reaction found. Again, it has been assumed that syphilis was exceedingly common in the marasmus type of infant admitted to a hospital. I remember many years ago while visiting the marasmus wards of the Blockley Hospital in Philadelphia, asking of the attending physician, who was showing me through the institution, what he did for this class of patients. "We give them all mercury and the iodids; they are all syphilitic," was his reply.

The presence in marasmus patients of enlargement of the liver and spleen and superficial lymph-nodes is not sufficient to warrant the diagnosis of probable syphilis. This is so often assumed that we have made the size of the spleen and liver a subject of special study in all patients examined. In the 167 negative cases the liver was much enlarged in 12 and palpable in 39 others. In the patients showing much enlargement of the spleen, the liver was almost invariably enlarged also, 7 of the cases showing much hepatic enlargement, and 8 of those showing splenic enlargement were rachitic.

There was general enlargement of the superficial lymph-nodes, sufficient to be noted, in fifty-two cases, or 33 per cent., and in twenty of these the swelling was considerable. It is evident, then, that mere swelling of the liver and spleen even when associated is not to be regarded as a very important sign suggestive of syphilis in infants suffering from malnutrition. Both are much more likely to be seen with rickets than with syphilis. Moreover, general swelling of the superficial lymph-nodes, whether occurring alone or with swelling of the liver and spleen, has no special significance. The only glandular swellings that do suggest syphilis are those of the epitrochlears when they occur without any peripheral lesion to explain it.

CONCLUSIONS

Cases of hereditary syphilis almost invariably respond positively to the Wassermann test, even when previously treated by mercury, unless the treatment has been very thorough and protracted.

After the use of salvarsan it has been my experience that it disappears much more regularly and earlier, but even then in most cases only after repeated injections.

Of 178 tests made in hospital patients showing no definite signs of syphilis, positive reactions were obtained in but eleven and five of these were shown on fuller investigation or subsequent findings to be pretty clearly syphilitic. Two of the remaining six were doubtfully so.

The great portion of congenital deformities have no relation to syphilis, since not a single positive reaction was obtained in fifty-six consecutive cases.

Of sixty-two patients suffering from malnutrition or marasmus, only five gave a positive reaction, and are included in the group above mentioned. Of the remaining fifty-seven, nearly one-third had very considerable enlargement of the spleen or liver, or both. Since the cases examined were selected from a much larger number, as those most likely to be syphilitic, we cannot regard syphilis as a common cause of marasmus, certainly in the patients admitted to the Babies' Hospital. Since the error, when one exists, is almost invariably on the positive side, the technic of those who find a very large proportion of positive reactions among marasmus patients in institutions is open to suspicion.

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THE LUETIN REACTION IN INFANCY *

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Stimulated by the discovery of the cutaneous skin test for tuberculosis, numerous observers, notably Wolff-Eisner, Neisser and Meirowsky, attempted to obtain a similar reaction specific for syphilis. These investigators used syphilitic extracts of liver, but their results on the whole were conflicting, owing to the fact that they obtained reactions with normal liver extracts, as well as those with extracts from syphilitic livers. This peculiar reaction toward normal liver extracts in syphilitic individuals, was described by Neisser as the state of *"Umstimmung,"* or allergic reaction. It was not till 1911 that Noguchi, using pure cultures of numerous strains of the *pallida* grown on solid media and then ground in a mortar, produced the substance known as *luetin.* By this process Noguchi claimed that not only spirochetes of different ages, but, in addition, the products of their metabolic processes, were obtained, and these factors he considered important in order to produce a state or condition of allergy or sensitization in persons supposed to be syphilitic.

The luetin as prepared by Noguchi is preserved in 0.5 per cent. trikresol. A syringe graduated in 0.5 c.c. is necessary. The skin is prepared as for the tuberculin skin test. The site chosen for injection is preferably the outer side of the upper arm, and the control, which consists of ground agar preserved in 0.5 per cent. trikresol, is injected into the opposite arm. The injection in each instance should be made intradermally, .05 c.c. being used. If the injection has been properly made the epidermis is raised to form a pale circle which disappears within a half hour; this happens with both the luetin and control.

With the injection used for control there is seen within eighteen to twenty-four hours a slight erythema around the point of puncture which disappears within two days. Where the luetin is injected there occurs within one to two days a red indurated papule, which slowly increases during the following four to five days, and then subsides, leaving a brown desquamating induration. This slowly disappears in the course of a few weeks. Occasionally, the indurated papule may go on to pustule formation.

Noguchi describes a torpid form in which nothing is seen till two or possibly three weeks after the injection, but which thereafter runs its usual course. This was not observed in our series of tests. With nearly

* From the service of L. Emmett Holt, M.D., The Babies' Hospital, New York.

every infant there was some variation in the degree of reaction, both as regards erythema and induration. The pustule, when present, was not larger than 2 or 3 millimeters in diameter. In many syphilitic infants the skin is very much thickened and indurated and in such cases the reaction is very difficult to interpret. This is also the case when the child is very anemic. It is in just such cases that faulty conclusions are apt to be drawn and it seems that in these instances the extent of the induration is of more value for diagnosis than the presence of the erythema, which may be very slight.

In all, 134 tests have been made at the Babies' Hospital. Thirty-four were in patients with hereditary syphilis, and 100 in controls. Of the syphilitic infants all but four gave a positive luetin reaction. In the 100 controls, ninety-six were definitely negative and four gave a doubtful reaction. All of the negative cases were also negative to the Wassermann test. In all the cases regarded as syphilitic the diagnosis was confirmed by the Wassermann reaction and the clinical history.

The reactions according to age were as follows:

	Positive Reaction	Negative Reaction
1 to 3 months	12	4
3 to 6 months	8	—
6 to 12 months	6	—
1 to 4 years	4	—
	—	—
	30	4

Of the syphilitic patients with a negative luetin reaction, all four were cases of severe infections and either the hemoglobin was very low or the skin much thickened so that one could not be certain of a positive reaction. Of the thirty positive luetin cases, fifteen showed small pustules; the other fifteen reacted in the form of a definite inflammatory papule. In addition it was observed that the more energetic the treatment the more distinct was the reaction. Especially was this the case after salvarsan injections.

The influence of treatment on the luetin reaction was as follows:

	No. of Cases	Positive Reaction
A. Salvarsan only	16	16
B. Mercury and salvarsan	3	3
C. Mercury only	5	5
D. No treatment	10	6

The cases used for control embrace a wide variety of pathological conditions. They were as follows:

	Cases
Marasmus	34
Pneumonia	22
Empyema	4
Tetany	3
Gastro-Enteritis	3

Two cases of each of the following: Spastic diplegia, cretinism, mongolian idiocy, eczema, rachitis, hernia, congenital heart disease, and tuberculous peritonitis. Total, 16.

One case of each of the following: Sclerema, bronchitis, retropharyngeal abscess, pemphigus neonatorum, scarlet fever, tuberculous meningitis, adenitis, Still's disease, nevus, cleft-palate, hare-lip, hygroma, mental deficiency, and tuberculous adenitis. Total, 14.

In none of these cases was a positive reaction obtained with the luetin test. Four other children gave a suspicious or doubtful reaction, but in only one was a positive Wassermann reaction obtained. This was a child 14 months of age, suffering from von Jaksch's anemia, who gave no clinical evidence of syphilis.

There were fourteen infants in whom the test was repeated after injections of salvarsan; of these, eight became negative during an average period of five months after the first injection of salvarsan. In each instance the Wassermann reaction corresponded with the luetin test, i e., it became negative at or about the same time. In the remaining six positive cases the reaction was present at the time of the last test made, which averaged three and a half months after the first injection of salvarsan. In this group also the Wassermann corresponded with the luetin test.

CONCLUSIONS

1. These observations indicate that the luetin cutaneous reaction is a valuable addition to the means of diagnosis of hereditary syphilis.

2. In the tests made in the hospital the results have corresponded closely with the clinical symptoms and the Wassermann reaction.

3. The luetin test has the obvious advantage that it can be readily applied anywhere by anyone and the technic is comparatively simple.

4. The interpretation of the reaction requires considerable experience, but with this the number of doubtful reactions is small.

RESULTS WITH SALVARSAN IN HEREDITARY SYPHILIS

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During the period extending from November, 1911, to January, 1913, there were treated in the Babies' Hospital thirty-four cases of hereditary syphilis by salvarsan alone. In all this series of cases the injections were given intravenously at the bend of the elbow. The technic was as follows: General anesthesia; a careful dissection of the vein and injection through a fine glass cannula which was substituted for the needle. In other respects the procedure followed was that usually observed in salvarsan injections.

This method of injection was found rather troublesome, tedious and somewhat difficult owing to the small size and fragile condition of the veins of these patients. The difficulties were, however, in a measure overcome with experience, and the time consumed in the operation was usually from fifteen to twenty minutes. In our later cases this method of injection was abandoned and the injections made with a needle directly into the external jugular vein. We used a 5 c.c. glass Luer syringe with a No. 22 gauge needle 1.5 cm. in length. The patient's arms were secured in a sheet and the head hyperextended and rotated to the side of the vein not used. The crying of the child caused the vein to stand out more prominently and facilitated the introduction of the needle. This plan of procedure was found quite satisfactory, except in very fat children. In them it is almost impossible to reach the vein without dissection. This has led us to try in recent cases the veins of the scalp, which have been found to be much more satisfactory than either of the preceding. Either the posterior auricular or one of the branches of the temporal vein may be used. These veins are readily entered on account of their bony and fibrous surroundings. The child is prepared as when the external jugular is to be used. Crying of the child and hyperextension of the head, make the vein more prominent. This method of injection has been found to have so many advantages over the others used that latterly it has been the only one employed.

The dose employed for infants up to 8 months of age was .05 gm. of salvarsan or 0.075 gm. of neosalvarsan; above this age, from .10 to .20 gm. of salvarsan or .15 and .30 gm. of neosalvarsan, according to the

age of the child, was given. A local reaction followed in but a single case, and in this there was only a slight induration, which persisted for a few days. In no instance were any untoward general symptoms observed as a consequence of the injection. The children usually were kept in the hospital for three or four days after the injections were made and were returned for subsequent treatment.

The patients injected were taken without selection, and they include all the patients with hereditary syphilis admitted during the period mentioned. No matter how hopeless the condition when the infant was brought to the hospital, it was given the benefit of the treatment in order to test the value of salvarsan in desperate cases.

Condition on Admission.—Only two of the thirty-four children were considered in good condition at the time of admission; twenty-two were in fair condition; six in very poor condition and four were in such a wretched state that they were regarded as hopeless, and lived less than three days. The weights, even better than this description, will give an idea of the condition of the children: Fourteen weighed 8 pounds or less; ten weighed between 8 and 10 pounds; and only ten were over 10 pounds.

Nineteen of the patients were under three months of age, four being under 1 month; eight were between 3 and 6 months; seven over 6 months, five of these being over 1 year old.

Only six of the children were exclusively breast-fed; four were partly nursed and partly fed; and twenty-four were bottle-fed entirely. This not only explains their bad condition, but also was an important factor in determining the results of treatment. With respect to severity of symptoms, seventeen were classed as severe and seventeen as mild infections.

Complete blood examinations were made in all the cases, the usual changes found being those of a secondary anemia of moderate degree. It is, however, of interest to note the marked eosinophilia present in three of the patients; the highest noted was 23 per cent. of the white cells.

Spirochetes were sought in twenty-one of the cases and were demonstrated in all but one of these. The stain employed was the Chin-Chin Pearly India ink, which has been found entirely reliable and simpler than the more commonly used Geimsa stain.

Wassermann tests were made in thirty-one children; all but one of these gave a positive reaction, this being a child who had been energetically treated with mercurial inunctions for a period of three months.

As generally administered, the dose of salvarsan we have used, .05 gm., is dissolved in 25 c.c. of distilled water. This amount is too large to be injected into one of the veins of the scalp or the jugular. By

experience we have found that 5 c.c. of water was sufficient and no irritation followed injections in this degree of concentration.

Repetition of Doses.—The plan followed has been a somewhat tentative one; we have been in the habit of giving the second dose two weeks after the first, and subsequent doses at intervals of from one to two months, being influenced by the result of the Wassermann test.

Results.—In estimating the effects of salvarsan in hereditary syphilis we have considered its influence on the spirochetes, the Wassermann reaction, the rash and other syphilitic symptoms and the patient's general condition. The examinations for spirochetes were made in most cases every second day, in a few cases daily, and in none at longer intervals than three days. The spirochetes disappeared on the average in four and a half days after the first injection; the shortest time was one day in one case and two days in another case. The longest time they persisted was thirteen days in a single case.

Circumstances did not permit our having the Wassermann reaction taken oftener than once a month, and in some of the patients only once in two months. In sixteen patients in whom frequent Wassermann tests were made, the average time of disappearance of the reaction was three and one-half months; the earliest being two months and the latest nine and a half months; the latter in a patient who had received four injections. In two patients positive reactions were obtained, one in two and the other in two and a half months subsequent to the negative reaction. One of these patients remained positive in spite of two later injections, and the other after a single injection. In five patients who were observed on the average for a period of three and one-half months, the positive reaction never disappeared, although one patient had four injections and four had two injections. The status of the cases as regards the Wassermann reaction at the time of latest report was as follows: Of thirty-four patients treated, seventeen had died and one was lost sight of; of the sixteen living, six were positive and ten were negative, the latter having been under observation for an average of ten months.

The effect of salvarsan is most strikingly seen on the cutaneous lesions. Patients admitted with profuse eruptions and moist lesions, especially of the face, often showed marked improvement in twenty-four hours, and within a week the skin, as a rule, was almost normal, only the pigmentation remaining.

The following case with the illustrations attached is a good example of what was often seen.

CASE REPORTS

CASE 1.—F. G., aged 1 month, admitted with a severe infection. The central part of face, mouth, nose, forehead and chin were covered with an intense maculopapular eruption and about the mouth were many crusts with moisture and

hemorrhage. The lower extremities were covered with a maculo-papular eruption as shown in the illustration (Fig. 1). The blood examination showed an eosinophilia of 21 per cent. The patient was given .05 gm. salvarsan. In twenty-four hours an improvement in the cutaneous lesions was evident, the eruption

Fig. 1.—Eruption of hereditary syphilis before treatment. (Case 1.)

drying up, the moisture and hemorrhage ceasing in a manner almost magical. By the fifth day the face, except for a few fissures about the mouth, was almost clear and the eruption on the extremities much less marked. The only signs were a pigmentation of the skin of the extremities marking the site of the old crusts and the cicatrices about the mouth and lips (Fig. 2). The eosinophilia

diminished in one week to 11 per cent. and in three weeks to 3 per cent. In one week after the first injection the spirochetes could no longer be demonstrated, The improvement in general condition was not less striking than in the eruption.

The effect of salvarsan in lesions of the bones is well shown in the following case of multiple dactylitis:

CASE 2.—R. N., aged 2 months, admitted with multiple dactylitis; no coryza or eruption, but a typical history of syphilis. The extent of the osseous lesions

Fig. 2.—The same patient five days after injection of salvarsan.

is shown in the x-ray pictures (Figs. 3 and 4) which portray marked changes in the first phalanges of the first and second fingers of the left, and of the second and third fingers of the right hand. In addition there was disclosed a similar lesion affecting the metacarpal bones of the second and fourth fingers of both hands. Externally the fingers showed only swelling, but no signs of acute

inflammation or breaking down. A dose of .05 gm. of salvarsan intravenously was given and repeated in two weeks. Within a week after the first dose there was an appreciable diminution in the size of the affected fingers and at the end of three weeks the hands were to all external appearances quite normal. The second radiograph was taken six weeks after the first and in it practically no traces of the previous lesion could be detected.

The effect of the treatment on the size of the liver and spleen was not so noticeable. Of nineteen patients who were followed long enough to make observations on this point possible, the size of the liver and spleen was unchanged in nine cases and markedly reduced in ten. Of seventeen patients in whom accurate observation of the lymph-nodes was possible, six showed definite reduction and no change was apparent in eleven cases. Improvement in the general condition of the patients as a rule corresponded to the change in the eruption, but was not quite so rapid nor so striking. In a few patients who were in very bad condition

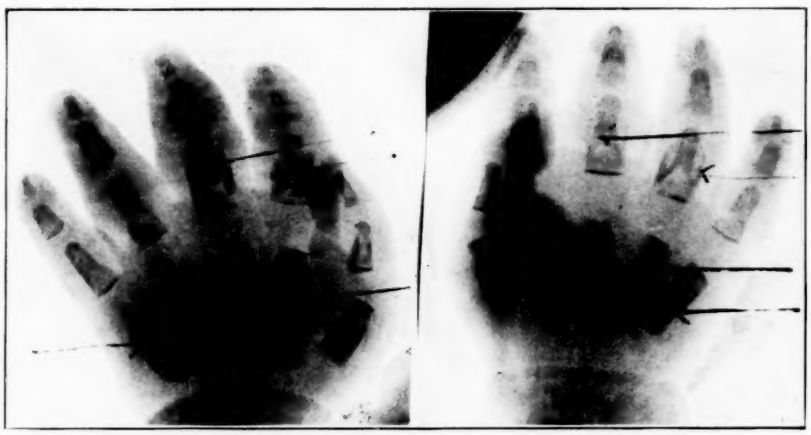

Fig. 3.—Syphilitic dactylitis before treatment. (Case 2.)

on admission, the injection of salvarsan was followed by marked retrogression in the cutaneous lesions without any corresponding improvement in the patients. Once begun, improvement in nearly all the patients continued unless the case was cut short by intercurrent disease. The following history is that of the only patient in whom a distinct relapse was seen in the syphilitic symptoms:

CASE 3.—T. M., aged 1 month, admitted with a severe infection, typical eruption and other symptoms of syphilis. Spirochetes were obtained from lesions about the buttocks and 0.1 gm. salvarsan was administered intravenously, followed by a second dose of the same size two weeks later. The symptoms and outward signs of syphilis rapidly disappeared after the injection and the child remained apparently well for two and one-half months when there was a recurrence of the eruption in typical form on the buttocks, and, as in the first instance,

the spirochetes were obtained from the lesions. A third dose, the same in size as in the two previous ones, was administered. This was followed as before by a rapid disappearance of the eruption and other symptoms. The child then remained apparently well for a period of three and one-half months when the eruption again appeared in a fairly typical form and the spirochetes were obtained from the lesions. A fourth dose was now given and four and one-half months later a fifth dose. There has since been no return of the symptoms.

Mortality and Causes of Death.—If both the early and late deaths from hereditary syphilis are included, the mortality is very high. Considering that the cases here reported were taken in routine, and considering also the condition in which a number of the infants were at the time of admission, a death-rate of 50 per cent. during the period of about nine months for which these infants were followed is not high.

Fig. 4.—The same patient as in Figure 3, six weeks after salvarsan injection.

These results are certainly much better than we have seen in the hospital with the same class of patients with any other treatment. Eleven of the deaths were from intercurrent disease, seven being from acute bronchopneumonia and three from gastro-enteritis; we have included these among the fatal cases, although in four death occurred in from three to nine and one-half months after treatment was begun, and probably syphilis was only very remotely responsible for the fatal termination. The proportion of deaths due to syphilis itself is better shown in the early deaths. Thus three patients lived one week or less, and nine from one week to one month. The accompanying table (Table 1) gives the causes of death and the time after first injection of salvarsan.

There was only one case in which any untoward general symptoms could be ascribed to the salvarsan. In this patient the symptoms, progress and termination of the case strongly suggested a multiple neuritis, which was attributed to the arsenic. The dose was twice that given to other patients. The evidence in this case was not conclusive, but the history is highly suggestive. A general autopsy was not permitted, but a microscopic examination was made of a section of the median and musculospiral nerves by Dr. Wollstein, pathologist to the hospital. Nothing abnormal was found.

TABLE 1.—CAUSES OF DEATH AND TIME AFTER FIRST INJECTION OF SALVARSAN

Case No.	Age	Cause of Death	Length of Time After First Injection
1	3½ mo.	Bronchopneumonia	4 days
2	5 mo.	Bronchopneumonia	1 week
3	7 wks.	Bronchopneumonia	3 weeks
4	3 wks.	Bronchopneumonia	1 month
5	3 mo.	Bronchopneumonia	1 month
6	1 mo.	Bronchopneumonia	3 months
7	2 mo.	Bronchopneumonia	9½ months
8	2½ mo.	Gastro-enteritis	1½ months
9	3 mo.	Gastro-enteritis	6 months
10	13 mo.	Gastro-enteritis	8 months
11	2½ mo.	Acute peritonitis	1 month
12	3½ mo.	Syphilis	15 hrs. after admission
13	6 wks.	Syphilis	2 weeks
14	2 mo.	Syphilis	3 weeks
15	5 mo.	Syphilis	1 month
16	6 wks.	Syphilis	1 month
17	5 wks.	Multiple neuritis	1 month

CASE 4.—M. P., aged 5 weeks, admitted in wretched condition, suffering from a severe syphilitic infection. August 9, 0.1 gm. of salvarsan was given intravenously and the same dose repeated August 26; there was marked improvement in the local lesions and general condition during these three weeks. Two days after the second injection the cry seemed feeble, and two days later a slight icterus was observed; this rapidly increased during the next twenty-four hours and at the same time there was a weakness of the upper and lower extremities, which increased to complete paralysis, with absence of the knee-jerks. Examination of the blood showed white blood-cells, 55,000; red blood-cells, 1,170,000; polymorphonuclears, 85 per cent.; lymphocytes, 14.6 per cent.; eosinophils, 0.3 per cent.; hemoglobin, 48 per cent.; many normoblasts, megaloblasts, megalocytes and microcytes. Red cells showed in addition considerable vacuolation. Urin-analysis revealed the presence of bile and occult blood. The general prostration and weakness steadily increased and five days after the paralysis was first noticed the child died apparently from respiratory involvement.

TABLE 2.—Table Showing Results of Treatment with

Case No.	Age.	Weight Lbs. Ozs.	Condition	Previous Treatment	Type of Infection	Spirochetes
1	1 mo.	9-5	Good	None	Severe	Present
2	10 mo.	17-0	Good	Mercury irregular for six months. (Inunct.)	Mild	Present
3	7 wks.	8-0	Fair	Mercury irregular since birth by mouth.	Mild	None found
4	3 mo.	11-5	Fair	None	Mild	Present
5	5 mo.	10-1	Poor	None	Mild	No external lesions
6	3½ mo.	7-2	Moribund	None	Severe	Present
7	1 mo.	7-11	Fair	None	Severe	Present
8	2 mo.	7-4	Fair	Mercury for one month irregular. (Inunction.)	Mild	No external lesions
9	3½ mo.	4-4	Bad	None	Severe	Present
10	2 mo.	5.8	Bad	None	Severe	Present
11	5 wks.	6-12	Fair	None	Severe	Present
12	2½ mo.	9-8	Fair	Mercury inunction off and on since birth.	Mild	Present
13	2 mo.	8-15	Fair	None	Severe	Present
14	13 mo.	8-15	Poor	None	Mild	No external lesions
15	5 mo.	10-8	Fair	Mercury inunction for 3 months.	Mild	No external lesions
16	2 mo.	7-7	Fair	None	Severe	Present

Date of Injection and Dosage	Wassermann	Result	Remarks
Nov. 21, '11—.05 gm. Jan. 11, '12—.05 gm.	Nov. 18, '11—Pos. Dec. 10, '11—Pos. Jan. 15, '12—Neg. Feb. 26, '12—Neg.	Died	Cause of death bronchopneumonia, Feb. 29, 1912. Free from all syphilitic manifestations and in good general condition before the final illness.
Dec. 7, '11—.05 gm. Apr. 3, '12—.05 gm. Jan. 9, '12—.10 gm.	Dec. 6, '11—Pos. Dec. 13, '11—Pos. Mar. 31, '12—Pos. June 29, '12—Pos. Oct. 10, '12—Neg.	Recovered	Examined in April, 1913. No syphilitic symptoms; in good condition.
Jan. 11, '12—.05 gm.	Jan. 9, '12—Pos.	Lost sight of	.....
Dec. 5, '12—.05 gm.	Dec. 3, '12—Pos. Dec. 13, '12—Pos.	Died	Cause of death bronchopneumonia, Dec. 28, 1912. Sick one week; syphilitic symptoms had disappeared.
Mar. 23, '12—.05 gm.	Mar. 20, '12—Pos.	Died	Cause of death bronchopneumonia, March 28, 1912. Sick one week. No improvement after injection.
Oct. 17, '12—.05 gm.	.....	Died	Fifteen hours after admission.
Dec. 10, '12—.05 gm. Dec. 29, '12—.05 gm.	Dec. 9, '11—Pos. Jan. 15, '12—Pos. July 10, '12—Neg. Sept. 1, '12—Neg.	Recovered	Examined in April, 1913. No syphilitic symptoms; in good condition.
Jan. 2, '12—.05 gm.	Dec. 25, '11—Pos. Mar. 30, '12—Neg. June 4, '12—Neg. Aug. 31, '12—Neg. Feb. 8, '13—Neg.	Recovered	Examined in April, 1913. No syphilitic symptoms; in good condition.
Apr. 13, '12—.05 gm.	Apr. 13, '12—Pos.	Died	Cause of death bronchopneumonia, fourth day after admission.
Apr. 13, '12—.05 gm.	Apr. 14, '12—Pos.	Died	In wretched condition on admission and died two days later of exhaustion.
Aug. 9, '12—.1 gm. Aug. 26, '12—.1 gm.	Aug. 9, '12—Pos. Aug. 31, '12—Pos.	Died	Cause of death multiple neuritis. Died twelve days after last dose. (Case reported in detail.)
Dec. 7, '11—.05 gm. Jan. 11, '12—.05 gm.	Dec. 10, '11—Pos.	Died	Cause of death acute gastro-enteritis, Feb. 1, 1912. Syphilitic symptoms had disappeared.
Dec. 16, '11—.05 gm. Jan. 2, '12—.05 gm. May 4, '12—.05 gm.	Dec. 15, '11—Pos. Mar. 30, '12—Neg. May 5, '12—Neg. May 15, '12—Neg. Aug. 4, '12—Neg.	Died	Cause of death bronchopneumonia, Aug. 12, 1912. Sick two weeks; syphilitic symptoms had disappeared.
Apr. 29, '12—.05 gm. May 8, '12—.05 gm. June 28, '12—.1 gm. Nov. 2, '12—.1 gm.	Apr. 28, '12—Pos. May 2, '12—Pos. June 27, '12—Pos. Aug. 11, '12—Pos. Sept. 8, '12—Pos. Oct. 10, '12—Pos.	Died	Cause of death, acute enterocolitis, Nov. 27, 1912. Sick one week; free from syphilitic symptoms and in good general condition.
Dec. 9, '11—.05 gm. Dec. 30, '11—.05 gm.	Dec. 8, '11—Neg.	Died	Cause of death, syphilis, Feb. 6, 1912. No improvement after injections.
May 24, '12—.05 gm. June 18, '12—.05 gm. Oct. 16, '12—.1 gm. Dec. 12, '12—.1 gm.	May 24, '12—Pos. Aug. 4, '12—Neg. Oct. 10, '12—Pos. Jan. 1, '12—Neg.	Recovered	Examined in April, 1913. No syphilitic symptoms; in good condition.

TABLE 2.—Table Showing Results of Treatment with

Case No.	Age.	Weight Lbs. Ozs.	Condition	Previous Treatment	Type of Infection	Spirochetes
17	2½ yr.	28-12	Fair	Mercury inunction irregular from birth.	Mild	No external lesions
18	3 mo.	8-12	Fair	None	Mild	Present
19	7 mo.	12-5	Fair	Mercury internally for one week.	Mild	No external lesions
20	21 mo.	21-15	Fair	Mercury and iodid irregular from birth.	Mild	No external lesions
21	4 mo.	11-4	Fair	None	Severe	Present
22	4 mo.	10-3	None	None	Mild	No external lesions
23	1 mo.	8-5	Fair	None	Severe	Present
24	6 wks.	9-5	Fair	None	Mild	No external lesions
25	3 wks.	7-0	Poor	None	Severe	Present
26	4½ yr.	32-0	Fair	Mercury by mouth irregular from birth.	Mild	No external lesions
27	1½ yr.	17-0	Fair	Mercury by mouth irregular from birth.	Mild	No external lesions
28	6 wks.	8-0	Bad	None	Severe	Present
29	7 wks.	7-0	Bad	None	Severe	No external lesions
30	4 mo.	7-8	Poor	None	Severe	Present
31	6 wks.	10-11	Fair	None	Severe	Present
32	6 wks.	5-8	Poor	Mercury inunction for two weeks.	Severe	Present
33	4 mo.	8-0	Fair	None	Mild	Present
34	2½ mo.	6-13	Poor	None	Severe	Present

SALVARSAN OF INFANTS WITH CONGENITAL SYPHILIS—*Continued*

Date of Injection and Dosage	Wassermann	Result	Remarks
May 11, '12—.1 gm. June 6, '12—.1 gm.	May 8, '12—Pos. June 4, '12—Pos. July 18, '12—Neg. Sept. 20, '12—Pos. Sept. 27, '12—Pos.	Recovered	Examined in April, 1913. Great improvement in general condition and free from syphilitic symptoms.
May 11, '12—.1 gm.	May 22, '12—Pos. July 1, '12—Neg. Oct. 10, '12—Neg.	Died	Cause of death acute gastro-entritis, Oct. 12, 1912. Free from syphilitic symptoms.
May 15, '12—.05 gm June 6, '12—.1 gm. July 6, '12—.1 gm. Dec. 12, '12—.1 gm.	May 15, '12—Pos. June 4, '12—Pos. July 1, '12—Pos. Aug. 4, '12—Pos. Oct. 10, '12—Pos. Dec. 13, '12—Neg. Feb. 23, '12—Neg.	Recovered	Examined in April, 1913. Great improvement in general condition and free from syphilitic symptoms.
May 5, '12—.1 gm. June 6, '12—.1 gm. July 15, '12—.2 gm. Dec. 12, '12—.2 gm.	May 15, '12—Pos. June 4, '12—Pos. July 1, '12—Pos. Aug. 31, '12—Pos. Oct. 10, '12—Pos. Dec. 13, '12—Pos. Feb. 23, '13—Neg.	Recovered	Examined in April, 1913. In good condition and free from syphilitic symptoms.
May 14, '12—.05 gm. June 6, '12—.1 gm. July 6, '12—.1 gm.	May 15, '12—Pos. July 1, '12—Pos. Aug. 4, '12—Neg. Oct. 17, '12—Neg. Feb. 23, '13—Neg.	Recovered	Examined in April, 1913. In good condition and free from syphilitic symptoms.
Aug. 11, '12—.1 gm. Aug. 26, '12—.1 gm. Oct. 17, '12—.1 gm.	Aug. 12, '12—Pos. Aug. 31, '12—Pos. Oct. 10, '12—Pos. Jan. 23, '13—Neg.	Recovered	Examined in April, 1913. In good condition and free from syphilitic symptoms.
July 15, '12—.1 gm. Aug. 13, '12—.1 gm. Oct. 3, '12—.1 gm. Jan. 22, '13—.1 gm.	July 20, '12—Pos. Aug. 3, '12—Pos. Jan. 23, '13—Pos.	Recovered	Examined in April, 1913. Great improvement; no syphilitic symptoms. (Case reported in detail.) Two relapses.
Apr. 29, '12—.05 gm. May 24, '12—.05 gm. July 6, '12—.05 gm.	May 1, '12—Pos. July 1, '12—Neg. Oct. 10, '12—Neg. Feb. 23, '13—Neg.	Recovered	Examined in April, 1913. Great improvement in general condition and free from syphilitic symptoms.
Sept. 23, '12—.05 gm. Oct. 13, '12—.05 gm.	Sept. 21, '12—Pos. Oct. 11, '12—Neg.	Died	Cause of death, bronchopneumonia. General condition fair; free from syphilitic symptoms.
July 23, '12—.2 gm. Sept. 9, '12—.2 gm.	June 1, '12—Pos. Sept. 8, '12—Pos.	Recovered	Examined in April, 1913. In good general condition and free from syphilitic symptoms.
July 23, '12—.1 gm. Sept. 9, '12—.2 gm.	June 1, '12—Pos. Sept. 8, '12—Pos.	Recovered	Examined in April, 1913. In good general condition and free from syphilitic symptoms.
Aug. 19, '12—1 gm.	Not done	Died	Cause of death syphilis, Aug. 26, 1912. Some improvement had occurred in cutaneous lesions.
Nov. 18, '12—.05 gm.	Nov. 8, '12—Pos.	Died	Cause of death, bronchopneumonia, Nov. 25, 1912. No improvement.
Dec. 11, '12—.05 gm. Jan. 4, '13—.05 gm.	Dec. 9, '12—Pos. Jan. 12, '13—Neg.	Recovered	Examined in April, 1913. In good general condition and free from syphilitic symptoms.
Jan. 8, '13—.05 gm. Jan. 22, '13—.05 gm.	Jan 25, '13—Pos.	Recovered	Examined in April, 1913. In good general condition and free from syphilitic symptoms.
Nov. 25, '12—.05 gm. Dec. 11, '12—.05 gm.	Not done	Died	Cause of death bronchopneumonia, Jan. 1, 1913. Doing well till onset of pneumonia and free from syphilitic symptoms.
Oct. 26, '12—.05 gm. Nov. 9, '12—.05 gm.	Oct. 26, '12—Pos. Feb. 23, '13—Pos.	Recovered	Examined in April, 1913. In good general condition and free from syphilitic symptoms.
Jan. 15, '13—.05 gm. Feb. 3, '13—.05 gm.	Jan. 23, '13—Pos. Feb. 8, '13—Neg.	Died	Cause of death acute streptococcal peritonitis. Marked improvement had occurred in syphilitic symptoms.

CONCLUSIONS

1. Immediate and striking benefit follows the injection of salvarsan in hereditary syphilis, and this is seen in many patients in whom mercury has been used with little or no apparent benefit.

2. Salvarsan must be given intravenously; with the technic which we have described its administration is not difficult and it is practically free from danger.

3. A single dose of salvarsan does not cure hereditary syphilis, although it often removes the visible symptoms. Relapses, however, are to be expected unless the dose is repeated. With present experience it seems advisable to repeat the injections at intervals for one year, even though no symptoms are present.

4. The best results in hereditary syphilis are undoubtedly obtained by the early use of salvarsan followed by mercurial treatment.

5. Even with the aid of the Wassermann reaction it is difficult to say when a child with hereditary syphilis is actually cured.

RESULTS OF TREATMENT WITH SALVARSAN IN LATE CONGENITAL SYPHILIS *

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During the past year we have treated with salvarsan eighteen children who were suffering from congenital syphilis. Our results as regards the Wassermann reaction were so surprising to ourselves that we searched the literature to ascertain the results of others and found so few reports controlled by the laboratory test that we think it worth while to report our cases.

Although the literature on salvarsan treatment is now enormous, very little work has been reported on its use in congenital syphilis. Among British writers, McDonagh[1] reports a case, aged 15 years, with disappearance of clinical signs, but with the Wassermann reaction positive after one dose. Sequeira[2] reports one case, also aged 15 years, in which he gave four doses of salvarsan intramuscularly; the remainder of his congenital cases were infants. In his cases the symptoms disappeared, but the reaction remained positive. He seldom gave more than one dose. Marshall[3] denounces salvarsan. Eddington and Browning[4] had a patient aged 16 years with a syphilitic knee. After two doses (0.2 and 0.27 gm.) of salvarsan the reaction became negative. Bunch[5] obtained a negative reaction in an infant of 8 weeks after two administrations, but an infant of 14 weeks was still positive after two doses.

In American literature the reports are merely reports of a few cases, and the effect of the Wassermann reaction is seldom mentioned. De Buys[6] reports three cases. He advises treatment through the mother's milk, and says salvarsan should only be used as an adjunct to mercury and potassium iodid.

The most thorough reports are by German and Austrian writers, but their reports are mostly on the treatment of nurslings through the

* Submitted for publication May, 1913.

1. McDonagh, J. E. R.: Brit. Jour. Child. Dis., October, 1910.
2. Sequeira: Brit. Jour. Child. Dis., February, 1911.
3. Marshall: Brit. Jour. Child. Dis., March, 1911.
4. Eddington and Browning: Glasgow Med. Jour., October, 1911.
5. Bunch: Brit. Jour. Child. Dis., April, 1912.
6. DeBuys: AMER. JOUR. DIS. CHILD., January, 1913.
7. Herxheimer and Reinke: Deutsch. med. Wchnschr., September, 1910.

mother's milk. Herxheimer and Reinke[7] report two fatal cases, both infants aged 2 months, and both dying four days after the administration. At autopsy arsenic was found in all the organs, but no treponema, except in the lungs, where they were agglutinated and markedly degenerated. Welde[8] treated twenty-eight patients, partly by subcutaneous and intramuscular injection, but his later cases by the intravenous method. His average dose was 0.1 gm., but most of his cases were in infants and received only one administration. The symptoms disappeared, but in only one case did the Wassermann become negative, and then it became positive again. No bad effects were observed.

We have treated eighteen patients; only three of these were under 5 years of age; most of them were suffering from bone lesions or interstitial keratitis. At the outset of our work, like most workers at that time, we believed that one or two doses would cure nearly all cases of syphilis, but by testing the Wassermann reaction after each administration we found it positive, and as the clinical symptoms did not entirely disappear in several cases we repeated the administration. Our method of procedure at first was to give salvarsan about once a month and test the reaction a month later. Later we gave a dose every week or every second week and tested the reaction usually between forty-eight and seventy-two hours following. We did not consider the reaction as finally negative unless the blood was tested between forty-eight and seventy-two hours after an administration, and we agree with McDonagh as to the value of a provocative dose, both in congenital and acquired syphilis. In ninety-nine administrations we used the intravenous method, except in one case (E. M.), who being mentally deficient, resisted, and we had to resort to intramuscular administration. To one who is experienced in giving intravenous injections the small veins of children do not offer a great obstacle. In most cases we used the median basilic or median cephalic veins, but occasionally we had to use the external jugular, placing the child in position advised by Wollstein and Morgan[9] for blood-culture work. In only one case, a marantic infant of 6 months, did we fail to enter a vein.

The amount given varied according to the weight of the child. Taking 150 pounds as the average male adult weight and 0.6 gm. salvarsan and 0.9 gm. neosalvarsan as average doses for that weight, we dissolved the salvarsan in 300 c.c. of distilled water and the neosalvarsan in 150 c.c. Of the latter we gave 1 c.c. and of the former 2 c.c. for each pound of weight of the patient.

8. Welde: München. med. Wchnschr., April, 1912.
9. Wollstein and Morgan: AMER. JOUR. DIS. CHILD., October, 1912.

THE CLINICAL RESULTS

The administration of salvarsan was in all cases followed by improvement in the physical signs. In no case did the symptoms resist repeated doses, although in one case (C. B.) there was a recurrence of symptoms one month after treatment had been discontinued, the patient having received nine doses. Three patients were babies suffering from wasting and rashes. All three were cured as regards symptoms. Seven patients suffered from interstitial keratitis. The inflammation of the cornea subsided in all cases, leaving, of course, scars, but the subsidence was at least as rapid as with mercury. C. B., aged 10 years, improved rapidly after the fourth dose and also showed marked improvement in his general health, but his symptoms recurred as mentioned above, and he again failed in general condition. Under mercury he improved again. He is the only patient in whom the treatment did not prove satisfactory. He also showed syphilitic arthritis of both knees, which was entirely cured, leaving no deformity. Seven of the patients were cases of bone syphilis, three affecting the nasal bones and causing severe ozena. The symptoms in all except the nasal cases subsided rapidly; one (R. D.) relapsed two months after her first dose, but her symptoms have entirely disappeared after four more doses. The nasal cases have all improved, but are slower and are still under treatment.

One patient had no symptoms except poor bodily development and Hutchinson's teeth. His Wassermann reaction was doubtful, that of his mother positive. He was only given one dose, after which his reaction was negative.

With the exception of R. D., all the children were under-sized and poorly nourished. The improvement in their general health was marked, resembling the improvement after operations in severe cases of enlarged tonsils and adenoids.

The only untoward results noticed were that three bone cases developed mild interstitial keratitis after treatment was begun, and one patient developed it in his right eye while undergoing treatment for the left. In no case were there severe symptoms following the administration, and after the neosalvarsan seldom any nausea at all. Some of them had vomiting for twelve to twenty hours after the administration of the original salvarsan.

THE EFFECTS ON THE WASSERMANN REACTION

As will be seen in the table, only five cases gave a negative reaction following treatment.

A. S., aged 6 months, was positive before treatment, received one dose of neosalvarsan and then for four months mercury by inunction. She then reacted negatively.

A. W., aged 17 months, reacted negatively after three doses, but his blood was not tested previously. His mother's blood was positive.

H. P., aged 12, reacted negatively after his eighth dose of neosalvarsan.

T. C., aged 12, received three doses of salvarsan and then three doses of neosalvarsan, after which he reacted negatively.

H. F., referred to above, reacted doubtfully before and negatively after one dose of neosalvarsan.

TABLE SHOWING EFFECT OF TREATMENT ON WASSERMAN REACTION

No.	Case	Age Yrs.	W. R. Before Treatment	Dose No.	W. R.	Dose No.	W. R.	Dose No.	W. R.	Dose No.	W. R.	Dose No.	W. R.	Dose No.	W. R.	Dose No.	W. R.
1	A. S.	5/12	+	1	|	2		3		4		5		6		7	
2	A. W.	5/12	+	1	:	2		3	|	4		5		6		7	
3	M. C.	5/12	+	1	+	2	+	3	:	4		5	+	6		7	
4	M. D.	5	+	1	:	2	+	3	:	4		5	+	6		7	
5	A. M.	6	+	1	:	2	+	3	+	4	+	5	+	6		7	+
6	R. F.	7	+	1	:	2	+	3	+	4	+	5		6		7	
7	H. P.	7	+	1	+	2	+	3	+	4	+	5	+	6	+	7	+
8	C. C.	9	+	1	+	2	+	3	+	4	+	5	+	6	+	7	+
9	W. P.	10	+	1	+	2	+	3	+	4	+	5	+	6	+	7	+
10	C. B.	10	+	1	+	2	+	3	+	4	+	5	+	6		7	+
11	T. C.	11	+	1	+	2	+	3	+	4	+	5	±	6		7	+
12	H. F.	11	±	1	|	2		3		4		5		6		7	+
13	P. S.	12	+	1	+	2	+	3	+	4	+	5	+	6	+	8	+
14	E. M.	13	+	1	+	2	+	3	+	4	+	5	+	6	+	8	+
15	R. D.	15	+	1	+	2	±	3	+	4	+	5	+	6	+	8	+
16	W. W.	24	+	1	+	2	+	3	+	4	+	5	+	6	+	8	+
17	F. E.	9	+	1	:	2	:	3	:	4	+	5	+	6	+	9	+
18	N. H.	7	+	1	:	2	:	3	:	4	:	5	:	6	+	9	+

The results of treatment on the Wassermann reaction can hardly be considered satisfactory, except as they compare favorably with the results obtained by mercurial treatment.

Gummata, periostitis and ulcers disappeared rapidly. Keratitis, which was present in eight cases, healed, we believe, more rapidly than under mixed treatment, and the resulting scars were therefore less. The results

were better than those obtained with mercury, and in about half of the cases followed treatment by mercury where the latter had been of little benefit.

Latterly we have used larger doses, and in future we shall use more intensive treatment, as large doses as the patient can stand and at shorter than seven-day intervals.

Nearly all the patients were treated in the out-patient department of the hospital and were sent home in a few minutes.

CONCLUSIONS

1. All our own cases improved clinically under salvarsan treatment.

2. The intensity of the Wassermann reaction diminished steadily with frequently repeated full doses, but in nine patients over 4 years, who received four doses or more, only two became negative, and that after eight and nine doses.

3. The younger the child, the more quickly does the Wassermann reaction become negative.

4. We have not found the administration of salvarsan by intravenous injection in children to produce any bad effects.

A RAPID CLINICAL METHOD FOR THE ESTIMATION OF TOTAL FAT IN INFANTS' STOOLS *

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One of the great disadvantages in the study of the digestive disturbances of infancy is our inability to determine quickly the quantity of fat present in an infant's stool. Qualitative tests, while of value, do not suffice, for under normal conditions we may encounter neutral fat, free fatty acids and soaps in an infant's stool. Our requirements will not be fulfilled until we have some approximate method for determining the neutral fats, free fatty acids and the soaps as they exist in the stool when it leaves the body, or, in other words, as they exist in the intestine uninfluenced by external agencies.

In pursuance of this need we began last September to study the various methods now in use for the estimation of fat in stools with the hope that we might find a way of shortening some of the existing methods, or of combining the different principles involved into a new or modified method. The methods we have investigated more in detail are the Kumagawa and Suto, Friedrich Müller, Keller's modification of Röhmann's and the Folin-Wentworth method. Hoffman's copper acetate method, a qualitative method with approximate relative quantitative possibilities, did not give us satisfactory results.

From our investigation we believe the Folin-Wentworth method comes the nearest being accurate of any of the methods considered. We base our opinions not on long or continued use of any of these methods, but on the principles involved. The Folin-Wentworth method, however, does not give us what we want. It determines only the neutral fat, the fatty acids, including the fatty acid of the soaps, and the total fats. If we regard the free fatty acids in the stool of little importance, as some have done, we may then regard the figures obtained for fatty acids as representing the soaps. We believe, however, that we are not justified in disregarding the free fatty acids, for under some conditions they are not insignificant. The Folin-Wentworth method is not a clinical method. It requires from twenty-one to twenty-four hours to complete it, providing the extracting apparatus can be kept running the full twenty-hour period. It is suitable for careful metabolism work, but even here there

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* From the Pediatric and Pharmacy Departments, University of Michigan.

* Read at the meeting of the American Pediatric Society, Washington, D. C., May, 1913.

are times, as we shall show later, when it fails to extract all the fat from a sample of stool.

One of us had been endeavoring for some time to develop a centrifugal method for the estimation of total fat. Being unable to get uniform results, we abandoned this method and directed our attention to an investigation of the rate of extraction with acid-ether according to the Folin-Wentworth method. Our results will be found in Table 1.

TABLE 1.—RESULTS OF EXTRACTION OF FAT FROM STOOLS BY THE ACID-ETHER METHOD

Sample 3. Pulverized Stool After Extracting.	Neutral Fat, Per Cent.	Fatty Acids, Per Cent.	Total Fat, Per Cent.	Total Fatty Substance, Per Cent.
Fractional Experiment*—				
One hour	1.73	17.69	19.42	37.20
Five hours more	0.02	22.36	22.38	42.87
Fourteen hours more	0.50	9.90	10.40	19.92
Total	2.25	49.95	52.20	99.99
Sample 3 extracted the full twenty hours	4.49	45.49	49.98	.....
Difference in total result...	+ 2.24	— 4.46	— 2.22	.....

* In this experiment a new weighed flask was substituted at the end of each run. The extraction was kept running the full twenty-hour period.

From this experiment it will be seen that the bulk of the neutral fat appears to be extracted at the end of the first hour, and the bulk of the fatty acids (produced by the action of the acid ether on the soaps) is extracted at the end of the sixth hour.[1] In other words, 76.88 per cent. of the neutral fat comes out in one hour, 82 per cent. of the fatty acids in six hours, and 80 per cent. of the total fat in six hours. It will be further observed that in the sample undergoing undisturbed extraction for twenty hours, over twice as much neutral fat is obtained and the amount of total fat is over 2 grams less than that obtained in the frac-

1. The formation of fatty acids from soaps is what is termed a substitution process. It is readily effected with weak acids. The following experiment shows how completely the acid ether extracts a sample of soap. We took of

Pure castile soap, gm.	1.1035
Extracted 12.5 hours with N/10 acid ether. Weight of substance after extraction, gm.	1.1142
Weight of substance unextracted by petroleum ether, gm.	0.0412
Fatty acids recovered from the soap. By subtraction, gm.	1.0623
By titration, gm.	1.0516

tional experiment. From this we conclude that the cold acid-ether process of extraction cannot be utilized for clinical purposes in the sense of giving us data on the three varieties of fat encountered in an infant's stool. We thought some importance might attach itself to the fact that the bulk of the neutral fat came out during the first hour's extraction, but the difference between the neutral fat figures for the fractional extraction experiment and the undisturbed twenty-hour extraction experiment is so great we feel that this process cannot be depended on for quick estimation of the neutral fat in a stool.

We next set ourselves the task of endeavoring to shorten the drying period. We encountered stools which dry more readily than others, and stools, which, in spite of many hours drying in the closed hot-air oven and subsequently many months (nine) desiccation over H_2SO_4, fail to remain in powdered form after passing through a forty-mesh sieve. We constructed a drying oven[2] through which a constant current of hot air passed, the stool sample being placed on a shelf over and under which the air circulated. By this method we were able to reduce the drying time one-half. Drying the stool with alcohol also shortens the period, and in many instances, but not in all, this method proved to be the shorter one. By this means the water is taken out with the boiling alcohol and the alcohol finally carefully evaporated off.

After the trial of other methods of extraction, hot alcohol, etc., and titration methods without, as yet, satisfactory results, we again turned our attention to our centrifugal method which determines the total fat only. At times we had succeeded in removing comparatively large amounts of fat from infants' stools by this method, while at other times with samples of the very same stool, and apparently exactly the same manipulations, we got only blank or negative results. The principle of the centrifugal method is the conversion of all fat and soaps into fatty acids, which are later brought into the graduated stem of a centrifugal tube and the amount in cubic centimeters read off directly.

In our effort to obtain uniform results three difficulties presented themselves:

1. A whitish substance almost invariably appeared floating on the surface of the centrifugalized fluid, and later it appeared below or

2. The oven is easily constructed. One length of Russia iron pipe 3½ to 4 inches in diameter is connected at each end with a circular elbow. At one end the elbow is turned down over a Bunsen burner, at the other the elbow is turned up and a thermometer suspended in it by means of a wire. An opening about 5 inches long is cut into the side of the pipe length and the flap turned into the pipe to form the shelf. A lid or door is hinged above the opening and is kept closed by means of a simple turn catch attached to the lower edge of the lid. The catch fits into a hole punched in the outer edge of the shelf flap. A brisk current of hot air passes through the pipe and the temperature is easily regulated with the ordinary Bunsen.

intimately mixed with the fat column in the stem of the tube after final centrifugalization. In some samples of stool in which no fat was present this substance rose to the top and sometimes resembled quite closely a poor fat layer.

2. Carbonization of the fat layer frequently took place because of an excess of acid. After a number of trials on different stools we were able to determine the maximum and minimum amount of acid necessary to burn the organic matter other than the fat and set the fat free, and to work out an optimum concentration which seems to be adaptable to most stools.

3. At times the fat column was difficult to read.

After milk fat passes through the intestinal canal certain physical changes take place. Before ingestion a centrifugal test shows a clear, fluid, yellow fat layer, which becomes more firm as it cools. It remains, however, in this clear condition for several minutes and is easily read. After the milk passes through the digestive tube a centrifugal test shows a denser and darker fat layer, which solidifies at a higher temperature and contracts in such a way as frequently to cause it to break in the center. A reading made when first taken from the machine is frequently a little greater than it is a minute or two later. If the tube is immersed in hot water the fat column melts and again occupies its former position in the tube. There is evidently a change in the specific gravity of the fat after it has passed through the intestinal tube. This difficulty seemed to be almost as insurmountable as the first one, which we will return to later. We thought to alter the specific gravity (lower the melting point) of the fat present in the stool by adding a known quantity of a fatty acid of low melting point. By deducting the difference in the result obtained we hoped to find the total fat content. We chose *oleic acid.* We were able to recover from stools and substances free from fat the amount of oleic acid added, and in stools with a fat content we were able to recover the oleic acid plus additional fat from the stool.[3] The fat column was by this means made clear. Such a method we believe is not acceptable from a chemical or clinical standpoint, for we are introducing a factor. The introduction into a stool of a substance sought might easily lead to error. We found, as we have stated, that much of our trouble with the fat column came from carbonization induced by adding too concentrated acid.

At this point in our investigation we came across Kita's[4] work on a similar method for the estimation of fat in meat. He had encountered the same difficulty with the appearance of a white substance on the top of the centrifugalized fluid, and found by adding a small amount of amyl alcohol complete separation of the fat layer was effected. We found

3. See foot note to Table 2.

4. Kita, T.: Arch. f. Hyg., 1904, li, 165.

this to be the case when we added amyl alcohol to our stool mixture. As is quite generally known, the addition of a small amount of 80 per cent. ethyl alcohol straightens out the fat column in the determination of fat in cheese by the Babcock method so that it can be easily read. Our experience with ethyl alcohol, however, has not been satisfactory. Because of its low boiling point (78 C.) when it is added to the hot acid stool mixture, some of the contents are often blown out through the stem of the tube. Kita gives no explanation for the use of amyl alcohol. The alcohol in either case effects a better separation of the fat, and we believe the advantage gained from the use of amyl alcohol lies in its very high boiling point (131 C.). By means of the addition of amyl alcohol, our fat layer now became as clear as we could wish it to be. By immersing the tube in hot water after centrifugalization the amount recovered is easily read off. As a precautionary measure we found it necessary that the amyl alcohol should be thoroughly mixed with the acid water stool mixture, otherwise it would come up into the stem of the tube, and, because of its acquired yellow color, appear as a fat column. We have worked out the following method, which has given us very uniform and apparently quite accurate results:

CENTRIFUGAL METHOD FOR ESTIMATION OF TOTAL FAT IN INFANT'S STOOLS

The Sample.—If pulverized stool is examined, one-quarter (0.25) gram should be carefully weighed. If fresh or moist stool is examined, one-half (0.5) gram. An inexpensive prescription balance is sufficiently accurate for clinical purposes. For more careful work an analytical balance is of course necessary. The stool, if dry, is best weighed in a poised watch glass and transferred to glazed paper. Moist stool is quite easily removed by means of a spatula from glazed paper on which it is weighed, or from the watch glass, by means of water. The sample is carefully rubbed up in a thin-lipped mortar. A maximum of 20 c.c. of warm (40 to 50 C.) distilled water is used to transfer the mixture to a Babcock milk bottle graduated in *fiftieths*. A little practice enables one to transfer the entire sample with the first 10 c.c. of water, leaving the remainder to rinse off the mortar and pestle.

1. To the sample, now thoroughly mixed, 17.5 c.c. H_2SO_4 (1.84) is added. Great care should now be taken to mix thoroughly by shaking the bottle back and forth vigorously (it should be remembered that all the organic material except the fat must be completely burned, or the test will be a failure).

2. One c.c. amyl alcohol is now added and thoroughly mixed.

3. The tube is now carefully counterpoised and centrifugalized for three minutes at high speed. Enough hot water is then added to bring

the fat into the graduated portion of the stem of the bottle. The bottle is again counterpoised, centrifugalized for one minute and the number of divisions on the stem occupied by the fat read off. Care must be taken to keep the stem hot and all readings must be made while it is hot. This is quickly accomplished by immersing the bottle in a pitcher or beaker of hot water.

Calculation.—If 0.25 gram of stool has been used, multiply the number of divisions on the stem of the tube occupied by the fat column by the factor 7.2; if 0.5 gram sample of stool is used, multiply by the factor 3.6; the result is the percentage of fat in the sample examined.

TABLE 2.—COMPARISON OF CENTRIFUGAL METHOD WITH FOLIN-WENTWOETH METHOD

Stool No.	Food Given.	Character of Sample	Percentage of Fat Obtained by the Centrifugal Method. Analysis No.				Folin Wentworth Method. Analysis No.		
			1	2	3	4	1	2	3
1	Eiweissmilch..	Pulverized.	36.00	36.00	36.00	.....	36.32	.....	.....
3	Eiweissmilch..	Pulverized.	43.08	43.23	.....	.....	49.98	52.20	.....
8	Eiweissmilch..	Pulverized.	36.00	32.40	32.40	32.40	34.52	35.24	.....
9	Breast milk...	Moist*	16.20	16.20	16.20	16.20	.....	.....	.....
11	Breast milk...	Pulverized.	50.40	50.40	50.40	.....	34.70	35.30	34.60
							Centrifugal test on sediment left in extraction capsule.....		14.40
									49.00

* Oleic acid method. By substituting 0.1 c.c. oleic acid for the amyl alcohol and rubbing it well into the stool we obtained with a sample of this stool 34.20 per cent. fat. Subtracting the oleic acid value, 18 per cent., we obtained exactly the same result, 16.20 total fat.

To determine the amount of fat in the twenty-four-hour sample of stool, the stools may either be weighed when passed, or they may be kept in a moist chamber and weighed at the end of the period. The former is the better method, for, by this means any loss or gain in weight may then be detected and accounted for. The stool from which the sample is taken must be thoroughly mixed. From the known weight of the stool the total amount of fat is readily estimated. With a little practice a complete test can be made in ten minutes.

Sensitiveness of the Centrifugal Test.—Table 2 records a few comparative tests with the Folin-Wentworth method.

It will be observed that in most instances the centrifugal method gives practically the same reading on the same stool. It is not subject to as many variations as the extraction method. It will be further observed that for some unexplained reason at one time it gave a lower percentage than the extraction method. In another rather striking instance the centrifugal method gave a much higher reading than the extraction method. In the last instance we were able to demonstrate that the acid ether failed to extract 14 per cent. of the fat after twenty-six hours' extraction in the Sohxlet apparatus, and that the addition of this amount to that previously obtained by the extraction method was almost the same as the figures obtained by our centrifugal method. Furthermore, in the case of the third analysis (No. 11), Folin-Wentworth, only 0.5 gram sample of stool was used and run for twenty-six hours, which is the equivalent of fifty-two hours on 1 gram, and yet we were able to extract no more fat than in the other two cases.

We believe the true fat content of this sample of stool would not have been known had we depended on the Folin-Wentworth method. This is the breast-milk stool previously referred to, which resisted pulverization, even after nine months' drying over H_2SO_4. After rubbing this sample through a fine sieve, it persisted in forming little balls and coffee-ground-like masses. These doubtless resisted extraction by the cold acid ether. The hot acid water mixture of course readily overcomes this difficulty. In the one case extraction is at work; in the other, liberation.

We believe a knowledge of the total fat content of stools may prove to be of value in the diagnosis and treatment of the digestive disturbances of infancy, and we hope this simple method, based on the Babcock principle, will help to further our knowledge in this field of medical research.

PROGRESS IN PEDIATRICS

RÉSUMÉ OF THE RECENT LITERATURE ON MENINGITIS (NOT INCLUDING MENINGOCOCCUS MENINGITIS)

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INCIDENCE

In 197 cases, Holt found the incidence of the various forms of meningitis as follows:

Tuberculous meningitis	138
Pneumococcus meningitis	22
Meningococcus meningitis (sporadic)	24
Staphylococcus and streptococcus meningitis	10
Influenzal meningitis	4
Bacillus coli meningitis	1
	199
Counted twice, mixed infections	2
	197

Tuberculous meningitis is, according to Holt,[1] twice as prevalent during March, April and May as in any other similar period. The number of cases increase in the spring, being highest during April. In summer and early fall, the lowest number of cases are seen. The most plausible explanation for the seasonal prevalence of tuberculous meningitis is that in these cases there had been a previous infection of the respiratory tract, usually of the bronchial nodes, which was latent. As a result of an acute respiratory infection, which occurs so commonly in the winter and spring months, the tuberculous process becomes active and spreads rapidly. This is apparently supported by the fact that at autopsy pulmonary lesions are invariably present, although in the great majority of the cases no pulmonary signs are demonstrable during life. The greatest number of cases are seen between the ages of 9 and 12 months. This may be due to closer exposure to infected adults at this period of life. In nearly all cases, exposure to pulmonary tuberculosis of the adult could be traced. This was also shown by a study of the type of the tubercle bacillus found in the cases of tuberculous meningitis. In 32 cases human bacilli were found in 30, bovine bacilli in 1, and both

1. Holt: AM. JOUR. DIS. CHILD., 1911, i, 26.

types in 1. From the number of cases of pneumococcus meningitis reported in the literature one might gain the impression that this form of meningitis is a frequent complication of pneumonia. Its infrequency, however, is well shown by the statistics of Rolly.[2] During 1904-1909, amongst 1,050 cases of pneumonia at the University Klinik at Leipzig, only 6 cases of pneumococcus meningitis were observed.

During the period of non-epidemic occurrence of meningococcus meningitis, 70 per cent. of all of cases of meningitis in infancy are, according to Morse, of the tuberculous variety.

The frequency of influenzal meningitis is shown by the fact that at the beginning of the year 1911, Martha Wollstein[3] was able to report on 49 cases of pure infections, and 9 cases of mixed infections. Of these, 28 were under 1 year of age; only 5 were in adults. Pisek, in 1912, speaks of 58 cases, only 5 of which were in adults.

PATHOLOGY

Oseki[4] has shown that when meningeal symptoms occur in the course of acute infectious diseases, the macroscopic examination of the nervous system alone is not sufficient to exclude the existence of organic changes. A careful microscopic examination often reveals the presence of a leukocytic infiltration of the meninges of the brain and cord. Not infrequently the same changes are demonstrable even when no meningeal symptoms have been observed during life. In a number of cases, inflammatory lesions were present in the parenchyma of the brain, but not in the meninges. In thirteen out of sixteen cases, Oseki found in the meninges or central nervous system, bacteria which were identical with those of the original disease.

Kirchheim and Schroeder[5] call attention to the fact that in acute infectious diseases, pathologic changes may be demonstrated in the central nervous system without there having been symptoms during life referable to the nervous system. It is, however, more common to find no changes where symptoms have been present. In these cases the symptoms are probably due to toxic action. It is still a question whether meningism is an early stage of meningitis. In some cases there seems to be some reason for this assumption, in others not. But up to the present, there is no direct proof of such a transition.

Rhein[6] made post mortem examinations on nine cases of meningitis; seven were diagnosed clinically and pathologically as tuberculous meningitis. One recovered from a tuberculous meningitis, but died one month

2. Rolly: Deutsch. med. Wchnschr., 1911, xxxvii, 774.
3. Wollstein: Am. Jour. Dis. Child., 1911, i, 42.
4. Oseki: Ziegler's Beitr. z. allg. Pathol., 1912, lii, 540.
5. Kirchheim and Schroeder: Deutsch. Arch. f. klin. Med., 1911, ciii, 218.
6. Rhein: Jour. Am. Med. Assn., 1912, lix, 165.

later of a pneumonia. The ninth case was one of pneumococcus meningitis. No tubercle bacilli were found in sections of the meninges and central nervous system. This is perhaps due to the fact that the sections were hardened in Kaiserling's solution. Blood-vessel changes as well as changes in the cortex were present in all. In three there was marked evidence of encephalitis. The author believes it possible, if not probable, that the exudate in the meninges is due to a mixed infection and not alone or at all to the tubercle bacillus. This explains the rapidity of the course, and the fact that in children the pathological lesions of the meninges does not resemble those of tuberculous meningitis occurring in patients succumbing to tuberculosis of other organs. The histologic picture in areas somewhat removed from a tubercle shows a round cell infiltration (simple inflammatory process as described by Villaret and Fixier, Peron, Hayen and Chantemesse). Diffuse infiltration without tuberculous granulations and without definite tubercles were described by Siredey and Tinel. The cellular changes are not typical. Plasma, lymphoid and phagocytic cells occur as in other inflammatory conditions. The vessels show thickening of the arteriole walls and some of the veins. Sometimes the lumina of these are obliterated. There is evidence of perivascular round cell infiltration. In some vessels the coats are thickened and there is cellular proliferation of the intima. Hektoen has described primary endarteritis and phlebitis with thrombosis and obliteration of the veins. The evidence of encephalitis was shown by distention of the perivascular spaces. In three cases there was present marked round cell infiltration of the superficial layers of the cortex. Plasma cells were seen in six cases.

Rhea[7] calls attention to the occurrence of extensive intraspinal hemorrhage in influenzal meningitis. In the brain substance an acute inflammatory reaction may take place about the blood-vessels. To these changes may be attributed some of the permanent lesions of the central nervous system which occasionally follow some of the acute illnesses associated with cerebral symptoms. Bacteriemia may develop in the course of influenzal meningitis. Organization of the exudate may lead to internal hydrocephalus. In chronic meningitis following the acute stage of influenzal meningitis the arteries of the meninges may show varying degrees of increase in connective tissue within the internal elastic membrane. Influenzal meningitis may be followed by paralysis of varying extent.

Davis[8] made post mortems in five of his seven cases of influenzal meningitis. In four there was an abundant highly purulent greenish-yellow exudate. In one case the exudate was less profuse and limited chiefly to the base and vessels of the Sylvian fissure. The exudate was

7. Rhea: Arch. Int. Med., 1911, viii, 133.
8. Davis: Amer. Jour. Dis. Child., 1911, i, 249.

abundant at the base and about the frontal lobes, leading to flattening of the convolutions. The cortical exudate occurred in large patches and was more abundant along the vessels. In one case, a pseudomembrane was seen along the inner surface of the dura which was red and congested. At the base thick greenish pus was found adherent to the dura. In one case a large subcortical abscess was found containing many bacilli. This abscess penetrated to the lateral ventricle. In the same case, there was softening of the cortex on the other side, but no abscess formation. Hemorrhage in the brain substance was not seen. In one case there was marked acute hydrocephalus. The exudate along the spinal cord was less marked than over the brain. It was more abundant along the posterior surface. Round cell infiltration, especially along the vessels of the substance of the cord, was seen penetrating into the gray matter. Pus was found in the central canal in two cases. Histologically, the exudate was rich in cells. Fibrin was either absent or present in traces only. Three types of cells were seen—polynuclears, mononuclears and large endothelial-like cells. The *Bacillus influenzae* was present in large numbers on the exudate. Small hemorrhages were occasionally seen. The walls of the blood-vessels were infiltrated and thrombosis was not rare. The exudate was situated on the deepest portions of the sulci, and for a short distance along the vessel into the cortex. But in this situation the infiltration was limited to a few polynuclear and plasma cells near the surface.

Acute rhinitis was present in 3 cases. In one there was extensive necrosis of the entire nasal mucosa involving the cribriform plate and downward into the pharynx. Acute bronchitis was present in 4 cases. In 3 cases there was evidence of bronchopneumonia along the posterior portions of the lungs, and more extensive in the lower lobes. The process in the lungs was distinctly lobular with infiltration of the peribronchial lymph channels containing a large number of plasma cells.

The bacilli were found in one case in the turbid peritoneal fluid. In another case there was a fibrinous exudate on the peritoneum and over the spleen originating from a splenic infarct. Acute degeneration of various viscera is not uncommon. In two cases, the bacillus was found in the heart's blood, in another case in the pericardial fluid. In three cases it was found in the bronchial secretion mixed with streptococci. In one case it was recovered from the surface of the nasal mucosa.

In a case of pneumococcus meningitis, which has now become classical, Holt[1] found at autopsy an old meningitis of the convexity in the exudate of which the pneumococcus was found. At the base the meninges were normal. Clinically, a perfectly clear and sterile fluid was found on lumbar puncture.

BACTERIOLOGY

Martha Wollstein[3] made an extensive study of the *Bacillus influenzae* as seen in influenzal meningitis. It was found to be a slender rod varying greatly in size and staining deeply at the poles. It is Gram-negative. It is invariably hemophilic and its marked characteristic is pleomorphism. The bacilli are usually present in large numbers in the cerebrospinal fluid. It usually occurs free, there being only slight phagocytosis. The organism did not grow on plain agar and sheep serum agar.

A culture of fifteen to twenty-four hours' duration shows minute regular bacilli among which a small number of threads are seen. On the second day, there is an increase in the number of curved forms and the threads are longer. The bacilli also increase in thickness. After seventy-two hours' growth many bizarre forms are seen.

Mice are highly susceptible to peritoneal injection. The peritoneum shows little exudate, the spleen is always swollen, the lungs and kidneys are congested. Bacilli are found in the heart's blood, peritoneum and other organs.

Small guinea-pigs (200 grams in weight) usually die within twelve to twenty-four hours after an intraperitoneal injection of ½ to 1 culture. There is an increase of peritoneal fluid which is turbid. Phagocytosis is rare. The spleen is two to three times its normal size. The kidneys are congested; likewise the lungs, which show areas of inflammation. The bacilli were found in pure cultures in the heart's blood and viscera. Organisms were also recovered from the surface of the pia of the brain and spinal cord.

Rabbits of 1200 grams weight, when injected in the ear veins, succumbed in fifteen to thirty-six hours. Small hemorrhages were found along the parietal peritoneum, within the serous coat of the intestines, beneath the capsule of the liver and along the pleura. The spleen is swollen and soft; the kidneys are much congested. The lungs showed areas of hemorrhage and inflammation. Positive cultures were obtained from the heart's blood, viscera, urine, surface of the cord and brain, and the mucous membrane of the upper nasal cavities.

The effect on monkeys will be described in the section on experimental meningitis.

Wollstein found all strains of the bacillus derived from cases of influenzal meningitis virulent for small animals, whereas those derived from the respiratory tract are not always so. The bacillus was recovered from the heart's blood in only four of the cases.

The agglutination reaction was found to be unsatisfactory. The determination of the opsonic index was but slightly more satisfactory.

In 1909, Cohen[9] reported several cases of meningitis due to a hemophilic bacillus, closely related to the *Bacillus influenzae*. It apparently differed from the latter organism in that it was highly virulent for rabbits, guinea-pigs and mice. It was present in the blood in all the cases, causing affection of the serous membranes. This observer claimed that it differed from the *Bacillus influenzae* in its agglutination and conglutination reactions. He called the form of meningitis due to this organism *meningite cerebrospinale septicaemique*. Similar cases were observed in France, Belgium, America and England. The same organisms were cultivated in a case of Prosek and Zatelli.[10] It is still a question whether this organism is to be regarded as a distinct species or merely a virulent form of the *Bacillus influenzae*.

EXPERIMENTAL MENINGITIS

By injecting through a trephine hole tubercle bacilli of established virulence for guinea-pigs and rabbits, Manwaring[11] succeeded in producing tuberculous meningitis in dogs. The disease was followed by paralysis and death. The effects of injection of suspensions of canine leukocytes were studied by this observer. His results will be described in another section.

Martha Wollstein[12] produced meningitis in monkeys (*Cercopithicus callitrichus* and *Macacus rhesus*) by injecting subdurally a virulent strain of bacillus influenzae. Symptoms usually appeared in five hours; the first evidence of disease being a disinclination to move actively. The cerebrospinal fluid became turbid and contained many bacilli. Death occurred from thirty-six hours to three to four days after inoculation.

Wollstein refers to the experiments of Cantani and Ritchie. Cantani injected influenza bacilli into the brain in rabbits. A non-lethal dose set up a chronic meningitis. Sometimes pus accumulated in the lateral ventricles. A microscopic examination showed an acute encephalitis.

Ritchie inoculated a *Macacus rhesus* with two blood-agar cultures in the lumbar region. The animal died eighteen hours later. At autopsy there was evidence of a beginning meningitis. Preparations from the surface of the cord and brain revealed numerous bacilli.

In Wollstein's animals a purulent exudate was found along the superior longitudinal sinus spreading laterally. There was a turbid exudate over the cord and the base of the brain. The exudate was marked at the site of inoculation. Smears from the pia arachnoid of the brain and cord showed a varying number of bacilli. On section there was seen a purulent leptomeningitis of the cord and the surface and

9. Cohen: Ann. de l'Inst. Pasteur, 1909, xxiii, 273.
10. Prosek and Zatelli: Wien. klin. Wchnschr., 1911.
11. Manwaring: Jour. Exper. Med., 1912, xv, 1.
12. Wollstein: Jour. Exper. Med., 1911, xiv, 73.

sulci of the brain. The exudate occurred chiefly about the blood-vessels. Innumerable bacilli were found among the pus cells. In one animal an influenzal empyema was found at the base of both lungs.

MENINGISM

Sachs[13] observed 16 cases of meningism amongst 400 cases of scarlet; 11 times it occurred in children 8 to 13 years of age; 3 times in children 2, 4 and 5 years of age, respectively. The condition was also twice found in adults. The most frequent symptoms were rigidity of the neck, hyperesthesia, change in mental condition and Kernig's sign. The Kernig sign persisted during the early period of convalescence. In one-half of the cases there was an increase of pressure in the cerebrospinal system, but there was no increase in albumin or abnormality in the sediment of the cerebrospinal fluid. The prognosis of meningism is always good and lumbar puncture seems to relieve the condition.

In cases of otitis, Schwartze[14] has at times observed stupor, continuous delirium and myosis. Immediate relief of these symptoms followed paracentesis of the inflamed drum. Schwartze refers to a case of Hicks where mydriasis, ptosis and paresis of one leg were completely relieved by tympanic paracentesis. Oppenheim, in his book, calls attention to the fact that a purulent otitis may be accompanied, especially in childhood, by brain symptoms resembling those of meningitis such as headache, vertigo, stupor, delirium and general convulsions. Even optic neuritis and paralysis of the abductus have been observed.

MENINGITIS SEROSA

Boenninghaus, in 1897, first drew attention to this condition as one of the intracranial complications of middle ear disease. Wagener observes that the symptoms may be latent. In marked cases the following symptoms may be present: headache, general malaise, vomiting, rigidity of the neck, Kernig sign, nystagmus, irregularity of pupils and increased tension of the pulse. One of the most constant symptoms is to be found in the fundus. In the mildest cases it may manifest itself as a unilateral hyperemia of the papilla and venous stasis. In the severe cases papillitis, choked disk and retinal hemorrhages are frequently seen. Wagener never observed primary optic atrophy.

TUBERCULOUS MENINGITIS

According to Holt,[1] the average duration of the disease after the onset of definite symptoms is two and a half weeks. Most of his patients had previously been in apparently good health. The v. Pirquet reaction was positive in 51 out of 65 patients. In 11 it was negative, and in 3

13. Sachs: Jahrb. f. Kinderh., 1911, lxxiii, Suppl., 68.
14. Schwartze: Arch. f. Ohrenhk., 1910, lxxxi, 77.

doubtful. Of these 14, four were moribund, and 7 extremely prostrated at the time the test was performed.

Riva-Rocci[15] observed four cases of tuberculous meningitis in children, 2½ years of age, that suffered from tympanites throughout the whole course of the disease. In two of these, there was found at autopsy an acute miliary tuberculosis of the peritoneum. In view of these findings, the author thinks that the presence of tympanites in tuberculous meningitis should lead us to suspect the existence of tuberculous peritonitis.

In infancy, Morse[16] has often observed an acute onset. The symptoms of spinal and cerebral irritation are less marked in this form of meningitis. It is rarely observed below 3 months of age. At this period of life, tuberculous meningitis runs an irregular course. Symptoms of irritation may be wholly absent. On the other hand, general flaccidity and diminished or absent reflexes are often observed. The duration is short. Morse has observed one case of only thirty-six hours duration. In infancy, remission of symptoms is less frequently seen than in later childhood.

Laparicinade[17] calls attention to the frequency of occurrence of tuberculous meningitis in infants below 2 years of age. Amongst forty-two cases collected from the literature not previously published, upwards of one-half were under 2 years of age. Three types of this disease are observed in suckling infants: eclamptic, hemiplegic and somnolent. In the eclamptic type, we observe after an initial convulsive seizure a rise of temperature, stiffness of the neck, more or less paralysis of hemiplegic or paraplegic form, followed by partial or general convulsions. Death usually occurs in two or three days during a convulsive seizure.

Hemiplegic form: An infant suffering from slight fever, develops more or less complete paralysis of one side of the body. Localized or general convulsions, stiffness of the neck and bulging of the fontanelle appear. The infant gradually falls into coma.

Somnolent form: This form is characterized by four cardinal symptoms: Progressive somnolence, ocular catalepsy, progressive emaciation, instability and irregularity of the pulse. The somnolence is progressive. At first the infant is taciturn, moody and depressed. It falls into normal sleep four or five times a day. At a later period the infant awakes only for drink. Ultimately deep coma develops.

Ocular catalepsy (fixity of gaze) is due to absence of winking. With it there is associated amblyopia and absence of conjunctival reflex. The infants sleep with wide open eyes, which have a vacant expression.

15. Riva-Rocci: Riv. di. clin. pediat., 1911, ix, 758.
16. Morse: Brit. Med. and Surg. Jour., 1911, i, 701.
17. Laparicinade: Med. Press and Circ., 1911, N. S., xci, 414.

The emaciation begins during the prodromal period. At the onset of the disease the only observable abnormality may be an instability of the pulse. The pulse may vary within short intervals, from 80 to 160. Vomiting and diarrhea, when present, are but slightly amenable to treatment.

When the disease is fully developed, the infant presents a characteristic picture. It usually lies on the back with wide-open, staring eyes. Conjunctivitis is a frequent complication. The temperature is usually subfebrile.

INFLUENZAL MENINGITIS

Among the 197 cases, Holt[1] observed four of influenzal meningitis, all of which were fatal. In 3 of the 4 cases, the organism was obtained from the bronchial secretion during life and in 2 from the nasopharynx. In 3, all those examined, it was found in the blood. In one case the *Bacillus influenzae* was found in the pus from an abscess of the elbow. A fatal influenzal meningitis developed later.

According to Pisek,[18] influenzal meningitis is characterized by severe constitutional symptoms which are out of proportion to the temperature curve. In this form of meningitis there is a rather sudden transition from symptoms of cerebral congestion to those due to intraventricular and subarachnoid pressure. Headache suddenly becomes more intense and there is pain on pressure over the eyes and supraorbital region. There is at first restlessness which is due to irritation of the sensory centers; later there is depression or abolition of the reflexes as a result of pressure. Convulsions may occur at the onset or paroxysmally during the course of the disease. There are usually present retraction and rigidity and slight opisthotonus. At this time there may exist an influenzal pneumonia, mild peritoneal irritation or involvement of the accessory nasal sinus. Albuminuria occurs in 0.6 per cent. At first there is tachycardia or arhythmia. Later the pulse is continuously high. There is steady emaciation. There may be delirium, stupor or profound coma. Severe convulsive seizures may occur at the beginning. Photophobia is often present. Other symptoms observed are irregularity of the pupils, loss of pupillary light reflex, nystagmus and neuroretinitis. The respirations vary with the stage of the disease and the condition of the patient. It is increased with high fever, sighing and shallow with stupor, irregular with coma. Cheyne-Stokes respiration is seen occasionally. The cerebrospinal fluid is uniformly cloudy, with a well-marked straw-colored sediment which shows a predominance of polynuclears and intra- and extra-cellular organisms.

Influenzal meningitis, according to Davis,[8] occurs sporadically, and there is no marked association with epidemics of influenza (la grippe).

18. Pisek: Am. Med., 1912, N. S. vii, 209.

It is confined largely to children under 1 year of age. The first authentic case in the literature was that of Pfuhl in 1892. Since then a large number of observers have reported on this disease, among them being Fraenkel, Ghon, Dubois, Adams, Cohoe, Cohen, Davis and Wollstein. Davis' report is based on seven cases, all of which were fatal. The duration of the disease varied from three to fourteen days. The youngest patient was 5 days of age, the oldest 13 months. There was a definite history of previous "colds" in four cases. The onset was indefinite, the early symptoms being cough, harsh breath sounds or definite signs of pneumonia. Eye symptoms were usually present as well as marked rigidity of the neck and retraction of the head. Definite convulsions were present in five cases. In all the children there was bulging of the anterior fontanel. In only one case was there herpes labialis. Some petechial hemorrhages were seen in one case just before death. The temperature varied from normal to 105 F. or higher, being subject to sudden change. The pulse was irregular, but rapid, 130 to 160. Apparently the period of incubation is not over five days, as two patients (twins) became ill within five days after birth. Lumbar puncture was performed on four patients. Cerebrospinal fluid was turbid, under high pressure and contained many leukocytes, 60 to 80 per cent. of which were polynuclears. The remaining cells consisted chiefly of small mononuclears. Endothelial cells were common. Red blood-cells were either absent or present in very small numbers. Fibrin was scant.

In one case the portal of entry was undoubtedly the nasal cavity as the infection could be traced through the necrotic cribriform plate of the ethmoid. In another case the bacillus was found in large numbers on the inflamed nasal mucosa. In two cases the infection probably originated in the upper respiratory tract.

Brem and Zeiler[19] observed two cases of influenzal meningitis which were treated with hexamethylenamin. The first case simulated an anterior poliomyelitis. There was no retraction of the head or marked stiffness of the neck. The Kernig sign appeared only one day before death. The Babinski was present from the first. Urotropin was given in 5-grain doses by intramuscular injection and 5 grains by rectum every four hours. Its presence in the spinal fluid was demonstrated by Herber's test. There was no apparent effect on the disease. In the second case meningeal symptoms did not appear until the sixth day of the disease. Five-grain doses of urotropin were given by intramuscular injection every four hours. Its presence could be demonstrated by the phenylhydrazin hydrochlorid test in cerebrospinal fluid diluted twenty times. By colorimetric test it was demonstrated in the cerebrospinal fluid in the strength of 1 to 3,750, in the urine in the strength of 1 to

19. Brem and Zeiler: Am. Jour. Dis. Child., 1911, i.

1,000. Hemoglobin appeared in the urine. Permanent drainage by means of a needle in the spine led to a fall of the temperature to normal. It remained so for twenty-four hours, until the needle worked out. There was no apparent effect from the administration of urotropin.

According to Leichtenstern,[20] influenzal meningitis usually appears at the height or rather at the beginning as a fulminating meningitis. The symptoms vary accordingly as it affects the convexity or the base of the brain. In the former case, which is the usual condition, there are intense headaches, absence of the rigidity of the neck and early loss of consciousness. When the base is affected the clinical picture closely resembles that of epidemic cerebrospinal meningitis, including herpes labialis.

PNEUMOCOCCUS MENINGITIS

Holt[1] reports on a very instructive case on a baby 20 months of age. There were fever, repeated convulsions and a leukocyte count of 24,000; there was no rigidity of the neck or extremities. Lumbar puncture on the first and seventh days yielded a perfectly clear fluid, showing no organisms on smears or cultures. During the third week, the child developed pneumonia with distinct signs of consolidation. On the third puncture, at this time 105 c.c. of fluid were removed, which again was negative. After the lapse of six weeks there were no active symptoms, but there was wasting and defective mentality. Death occurred in the eleventh week from a second attack of pneumonia. At autopsy there was found an old meningitis at the convexity in the exudate of which pneumococci were demonstrated. In eight of twenty-two of Holt's cases, the duration of the disease was three days or less. In two-thirds of his cases it was six days or less. The diagnosis of this form of meningitis presents great difficulties, as the lesions are occasionally localized at the convexity. As a result of this localization such characteristic symptoms as opisthotonos, irregularity of the pulse and respirations, distention of the fontanel and involvement of the cranial nerves may be absent. Pneumococcus meningitis occurs in younger children than either epidemics of cerebrospinal meningitis or tuberculous meningitis. One-half of Holt's cases were under 6 months of age, two-thirds of them under 9 months.

According to Schlesinger,[21] pneumococcus meningitis may have either an apoplectic, acute, subacute or insidious course. The fever in favorable cases is less high and of shorter duration than in epidemic cerebrospinal meningitis. Rapid euphoria appears after cessation of fever, despite the persistence of meningitic symptoms.

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21. Schlesinger: Wien. med. Wchnschr., 1911, lxi, 40.
20. Leichtenstern and Stricker: Influenza, Wien and Leipsic, 1912.

According to Rolly,[2] the mode of invasion of meningococcus meningitis is dependent on the portal of entry; 8 of his 30 cases began with or after a pneumonia or bronchitis; 6 with sepsis and endocarditis; 3 with otitis media; 9 with rhinitis or disease of the accessory sinus, 1 after trauma. In 3 cases the cause was unknown. In the 26 fatal cases, the disease began with slight prodromata, lasting one to seven days. These consisted of headache, backache, general malaise, anorexia, dizziness and occasional vomiting. In 5 cases no premonitory symptoms were present, but the disease began with fever, vomiting, agonizing headache and marked vertigo. Only once was a chill present. Rigidity as well as pain on moving the head was constant. The Kernig sign was pronounced. Herpes was rather unusual. The cases exhibited marked restlessness and early loss of consciousness. In 3 cases clear cerebrospinal fluid was obtained in which pneumococci were seen. The duration of the disease varied from two to twenty-five days.

OTHER SUPPURATIVE MENINGITIDES

Two cases of meningitis due to *Bacillus coli* were observed by Holt.[1] The first was a baby 4 weeks of age, which was admitted to the hospital with Erb's palsy and malnutrition. During its stay it developed the usual symptoms of meningitis with a temperature up to 103, general hyperesthesia and rigidity and a leukocyte count of 13,000. The disease ended fatally after ten days' illness. The second infant was also 4 weeks of age; there was a previous history of *Bacillus coli* infection of the urinary tract. The patient recovered from the acute symptoms, but developed a secondary hydrocephalus. A case of typhoid meningitis was observed by David and Speik.[22] One due to paratyphus infection by Boonacker and Gorter. One of infection by the Friedlander bacillus by Guinon and Simon[23] (recovery in four days). Of ten cases of pyogenic (staphylococcus or streptococcus) form, six were seen by Holt in newborn babies. In five cases the meningitis was secondary to spina bifida. In one the meningitis followed an operation for hydrocephalus. In only two was the meningitis apparently primary clinically, the development was rather rapid, being accompanied by severe general and local symptoms. The termination was always unfavorable. Only once did a meningitis follow an otitis or its complications. This was in a 15-months-old child on whom a double mastoid operation was performed, in Europe. The dressing was unchanged for nearly two weeks; that is, during the trip across the ocean. The discharge was very foul and the wound in bad condition. At autopsy, however, there was found no connection between the mastoid and the meninges. The meningitis was of the tuberculous variety.

22. David and Speik: Jour. Am. Med. Assn., 1911, lvi, 882.
23. Guinon and Simon: Bull. et mem. Soc. d. hôp. de Paris, 1910.

Remlinger[24] describes cases of aseptic meningitis in which there was turbid or purulent fluid without any organisms being demonstrable.

DIAGNOSIS

Lucas[25] gives a detailed discussion of the diagnostic value of the cerebrospinal fluid in various cerebral affections. He shows that the cytology in tuberculous meningitis is not characteristic, as a similar picture is seen in a number of cerebral affections, such as encephalitis, myelo-encephalitic meningism, syphilis of the meninges and arterior poliomyelitis. In myelo-encephalitis, both experimental and human, the cerebrospinal fluid was turbid, contained fibrin and showed a large number of mononuclear cells or lymphocytes. In 248 cases of tuberculous meningitis, the amount of fluid varied from 5 to 120 c.c. In some cases it was clear, in others opalescent. Occasionally the fluid was turbid. There was no clot formation in a little over 10 per cent. But it was present some time or other in every case. The number of cells per cubic millimeter varied from 14 to 920, the average being 206. Fifty per cent. of the cases had 100 cells or below. The differential count showed a variation from 100 per cent. lymphocytes and mononuclears to 89 per cent. polynuclears. In twenty-five instances the polynuclears numbered 30 per cent. or over.

In 102 cases of pyogenic meningitis the amount of fluid varied from a few drops to 250 c.c. In three cases the fluid was clear. Clot formation was always present, except in clear fluid; the number of cells varied from forty-five to 2,600 per cubic millimeter. There was always a preponderance of polynuclears. In chronic cases the mononuclears equalled or were in excess of the polynuclears. The cytology alone is therefore not sufficient for the separation of the various forms of meningitis.

The diagnosis of tuberculous meningitis rests, according to Dunn,[26] on a triple basis, namely, clinical character, examination of the cerebrospinal fluid, and the invariably fatal termination. No one of the characteristic symptoms and signs is invariably present. The onset may be sudden or gradual; the temperature high, moderate or low. Unconsciousness may appear rapidly during the early stages or slowly and at a late period. The following symptoms may be present or absent: headache, rigidity of the neck, Kernig sign, localizing neurological signs, convulsions, vomiting and leukocytosis.

The characteristics of the cerebrospinal fluid are of greater value than the clinical picture. In sixty cases which the author analyzed, a predominance of lymphocytes was constantly present. But such a lymphocytosis may be present in other conditions. Determination of the number

24. Remlinger: Gaz. d. hôp., 1911, lxxxiv, 1125.
25. Lucas: Am. Jour. Dis. Child., 1911, i, 230.
26. Dunn: Arch. Pediat., 1910, xxvii, 685.

of cells by the centrifuge is an inaccurate method. The author advises that the number of cells should be estimated by the use of the white blood counting pipet. The staining mixture given below is drawn up to the 0.5 mark of the white blood counter, the fresh cerebrospinal fluid is drawn up to the 11 mark. The ordinary blood counting slide is used. The number of cells counted on ten slides represents the number of cells per cubic millimeter. The staining mixture used is as follows:

	Gm. or C.C.
Methylene violet	0.1
Acetic acid	2.0
Water	50.0

Glacial acetic acid alone may be used. The number of cells found in normal fluid by this method varies from none to three cells per cubic millimeter. Ten cells, however, are taken by the author as the limit of a normal count.

In 60 cases of tuberculous meningitis, representing 71 examinations, there was a count above normal in all cases. The lowest count was 30, the highest 920. In the following conditions the cell count was normal — lobar pneumonia, anterior poliomyelitis, typhoid, solitary tubercle, cerebellar tumor, cerebral hemorrhage, rheumatic fever, otitis media, measles with pneumonia, gastro-enteric intoxication. In one case of tetanus there was a cell count of 60. The cell count is of special value in the differentiation between tuberculous meningitis and cases of gastro-enteric disturbance and toxic absorption. The author did not find any definite relation between the stage of the disease and the number of lymphocytes.

Hemenway[27] found tubercle bacilli in the cerebrospinal fluid in 135 out of 137 cases. In one of the negative cases only 2 cubic centimeters of fluid were obtained; in the other the fluid was withdrawn at an early stage of the disease. The technic of the author is as follows:

> The cerebrospinal fluid is collected in several test-tubes, about 20 c.c. in each tube. The last fluid after the child is set up is the most important. The tube should not be shaken as the fibrin film or coagulum forms more readily when the tube is not disturbed. The tubes are placed in the incubator; after ten hours the film can be removed entire with a platinum loop. It is then spread out carefully with fine needles on a glass slide. It is then fixed and stained by Sabbet's method.
>
> In about 40 per cent. of the cases no coagulum forms. In these cases the sides of the test-tube are scraped with the platinum loop and any material removed is superimposed drop by drop over a small area on a glass slide. Each drop is dried in the air and fixed in the flame before another is added. The sediment from the test-tube may be superimposed by means of a fine capillary tube in the same manner. If no coagulum forms and no tubercle bacilli are found in the first puncture fluid, the needle on the second puncture, just before being withdrawn, is pushed slightly forward so as to touch the anterior surface and

27. Hemenway: Am. Jour. Dis. Child., 1911, i, 37.

1 or 2 drops of blood are allowed to flow in the last tube. This aids in the formation of a coagulum. The tubercle bacilli are more numerous at a late stage of the disease.

Netter and Gendron,[28] in their observation on the cytodiagnosis of tuberculous meningitis, find that in childhood there is an average of 100 lymphocytes to the cubic millimeter. In poliomyelitis there are about twenty lymphocytes to the cubic millimeter and in other meningeal conditions three to fifteen lymphocytes per cubic millimeter.

In acute meningitis and in progressive paralysis, Weil and Kapka[29] found the meninges permeable to sheep hemolysins. In acute meningitis, the total hemolysin (amboceptor and complement) is demonstrable. The degree of reaction depends but slightly on the varying degrees of permeability of the meningeal vessels, but rather on the abundance of hemolysins in the blood.

Strouse[30] finds the Noguchi reaction (butyric acid reaction) positive in all meningitis cases. It was negative in three cases of meningism.

Trembur[31] found that incubation of the cerebrospinal fluid in sealed test-tubes at 37 F. for twenty-four to seventy-two hours, greatly increases the number of tubercle bacilli.

Tinel and Gastinel[32] describe a number of meningeal states in tuberculosis. In one group the patient suffers from attacks of headache every evening. There are in addition slight vomiting, rigidity, Kernig and transitory changes in pulse and temperature. Lumbar puncture, which relieves the symptoms, immediately yields a cerebrospinal fluid, which, though usually normal, occasionally shows a slight increase in albumin and lymphocytes; no tubercle bacilli are found.

In another group, there are in addition to the above symptoms, sciatic pain, which is due to anatomical changes in the nerve, as a healed tubercle or cyst.

In a third group, the intensity of the symptoms leads one to suspect tuberculous meningitis, but the condition gradually improves. There may be several attacks of gradually lessening severity. The cerebrospinal fluid shows moderate lymphocytosis, but it may be entirely negative. At autopsy, there is found a diffuse sclerosis of the meninges without signs of recent inflammation.

PROGNOSIS

Undoubted cases of recovery from tuberculous meningitis have been recorded in the literature by a number of observers, amongst these being Freyhan, Henkel, Barter, Gross, Claisse and Abrami, Riebold, Rumpel,

28. Netter and Gendron: Bull. Soc. de pédiat. de Paris, 1911, p. 226.
29. Weil and Kapka: Med. Klin., 1911, vii, 1314.
30. Strouse: Jour. Am. Med. Assn., 1911, lvi, 1171.
31. Trembur: Klin. Jahrb., 1911, xxiv, 359.
32. Tinel and Gastinel: Rev. de méd., 1912, xxxii, 4, 241.

Stark, Archangelsky, Hochstetter and Dunn. These observers found the tubercle bacilli in the cerebrospinal fluid.

Autopsy evidence of a previously existent tuberculous meningitis have been found by Jannssen, Thomalla, Weermann and Leube.

Cases of recovery from pneumococcus meningitis are recorded by Jemma, Hauer, Kohts (two cases), Grober, Schlesinger[21] and Rolly.[2]

TREATMENT

Martha Wollstein[12] succeeded in immunizing a goat with bacillus influenzae. The blood acquired moderate agglutinating and high opsonic power. Injected in the spine it arrested the progress of the experimental meningitis and brought about recovery. As a result of the injection of the serum, the bacilli were more freely engulfed by the phagocytes. The number of the organisms became reduced, their capacity for growth diminished, and their entrance into the blood arrested. This led to a cessation of the local inflammatory process and progressive amelioration of the symptoms. At first, the serum was injected after one hour's inoculation of the bacilli. Later successful results were obtained even when the serum was applied twenty-four hours later.

Manwaring[11] inoculated dogs subdurally with tubercle bacilli of established virulence for guinea-pigs and rabbits, and succeeded in producing a tuberculous meningitis. The disease was followed by paralysis and death. When suspension of canine leukocytes was injected subdurally, the onset of the paralysis was delayed, and the life of the animal was prolonged. With large doses of tubercle bacilli, the injection of leukocytes had no effect. With small numbers of very virulent bovine bacilli, the leukocytes uniformly produced a prolongation of the latent period. But they had a less evident effect on the subsequent course of the disease. All the animals died.

With small doses of less virulent human bacilli, half of the animals did not develop paralysis. The others developed paralysis after a much prolonged incubation period, from which one animal died. In some of the treated dogs, the tuberculous lesions in the upper part of the subdural space had apparently been arrested or caused to undergo resolution. In the lower third of the spinal cord, the lesions persisted or advanced to a chronic condition.

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